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ABSTRACT

This booklet describes only a glimpse of what is known about the nervous system, brain disorders, and the exciting avenues of research that promise new therapies for many of the most devastating neurological and psychiatric diseases. The neuron, brain development, sensation and perception, learning and memory, movement, advances and challenges in diseases such as Parkinson's disease, major depression, and stroke, new diagnostic methods, and potential therapies are topics of discussion. (KR)

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BRAIN FACTS

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

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SOCIETY FOR NEUROSCIENCE
11 Dupont Circle, N.W. • Suite 500 • Washington, D.C. 20036 • 202-462-6688

October, 1990

Dear Reader:

Welcome to Brain Facts.

This booklet, approved by the Society for Neuroscience governing Council in October, 1989, is intended to provide an introduction to the brain and nervous system and their disorders. It is one part of the Society's continuing effort to educate the public about neuroscience.

Designed for use by high school biology teachers and science reporters, Brain Facts also can be used in libraries, schools, colleges and homes by anyone who needs to read, write, teach or learn about the brain.

While Brain Facts spans a wide range of neuroscience, it does not pretend to and cannot cover everything in depth or all subjects that are relevant. The Society plans to update Brain Facts as the pace of research warrants.

I hope you find it useful.

Sincerely,

Patricia S. Goldman-Rakic

Patricia S. Goldman-Rakic, Ph.D.
President

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INTRODUCTION

It has allowed humans to dominate all other species, walk on the moon and compose masterpieces of literature, art and music. Throughout recorded time, the human brain — a spongy, three-pound mass of gray and white matter — has been compared to a radiator to cool the blood, a telephone switchboard and a supercomputer.

But the brain is much more complicated than any of these, a fact scientists are confirming almost daily with each new discovery. The extent of the brain's capabilities is unknown but it is certainly the most complex living structure we know of in the universe.

This single organ directs the major acts of living. The brain controls all bodily activities, ranging from heart rate and sexual function to emotion and learning. It is even thought to influence the body's immune system response to disease and how well people respond to medical treatments. Ultimately, it shapes our thoughts, hopes, dreams and imagination. In short, it is what makes us human.

As early as the sixth century, B.C., when Greek philosophers suggested it was the "organ of the mind," humans have been trying to understand the brain. By the 17th century, the brain's general outline became clear through anatomical examinations. Rigorous study was stimulated in 1891 with the formal pronouncement that the nervous system was made up of nerve cells.

Neuroscientists, who represent a relatively young field of science, have the daunting task of deciphering the mystery of the most complex of all machines: how some 200 billion nerve cells and a trillion supporting cells are produced, grow and organize themselves into effective, functionally active systems that stay in working order throughout a person's lifetime.

The motivation of researchers is twofold: to understand ourselves better — from how we learn to why people have trouble getting along together — and to discover ways to prevent or cure many devastating brain disorders.

Indeed, the more than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, including heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually at costs exceeding $120 billion. Mental disorders strike 19 million adults a year at a cost of some $104 billion. Children also suffer. Hundreds of thousands of young Americans are affected by mental retardation, behavioral disorders and developmental problems that have no cure.

Much has been uncovered about these and other disorders and the brain itself during the last two decades. Key to this progress has been better ways of examining the nervous system. New techniques, including the powerful tools of molecular genetics, now promise to uncover even more.

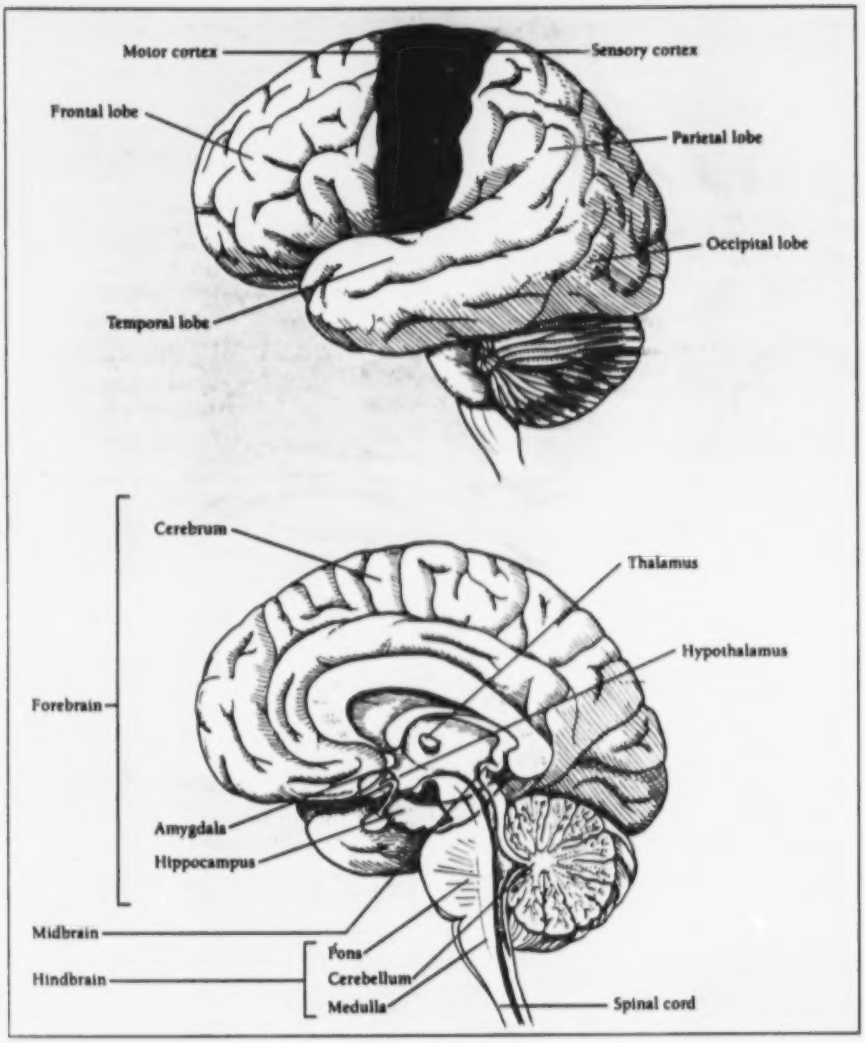
The Congressionally-designated Decade of the Brain, which began in 1990 with annual federal neuroscience research support of roughly $1.2 billion, should greatly expand our knowledge of the brain. During this decade, basic scientists are focusing on the nervous system's fundamental workings while clinicians are studying better ways of caring for patients with brain disorders.

Improved methods of prevention, diagnosis and treatment are sure to follow. On the horizon are new drugs for neurological diseases and artificial sensory systems for damaged hearing and sight. Scientists are rapidly discovering gene markers for many hereditary neurologic and psychiatric diseases. Ultimately, researchers hope to discover the biochemical defects these genes control so they can prevent or correct them.

Neuroscientists have identified major areas of extraordinary promise: how the brain develops and maintains itself; how it acquires, stores and uses information; how it regulates the body; how it expresses rhythms, drives and emotions; and what is altered in the brain by neurologic and mental disorders.

Our understanding of the brain still contains many gaps in knowledge. At best, our comprehension of perception, learning, memory, language and mood is rudimentary. But the methods are available to understand these processes.

This booklet describes only a glimpse of what is known about the nervous system, brain disorders, and the exciting avenues of research that promise new therapies for many of the most devastating neurological and psychiatric diseases.



BRAIN. Cerebral cortex (above). This part of the brain is divided into four sections: the *occipital lobe*, the *temporal lobe*, the *parietal lobe* and the *frontal lobe*. Functions, such as vision, hearing and speech, are distributed in selected regions. Some regions are associated with more than one function. Major internal structures (below). The *forebrain* is credited with the highest intellectual functions — thinking, planning and problem-solving. The *limbic system* — the *amygdala*, *hippocampus*, and *septum* (which is not shown here) and parts of the cortex — all help regulate emotion, memory and certain aspects of movement. The *thalamus* serves as a relay station for almost all the information coming into the brain. Neurons in the *hypothalamus* serve as relay stations for internal regulatory systems, monitoring information coming in from the autonomic nervous system and commanding the body through those nerves and the pituitary. On the upper surface of the *midbrain* are two pairs of small hills, *colliculi*, collections of cells that relay specific sensory information from sense organs to the brain. The *hindbrain* consists of the *pons* and *medulla*, which help control respiration and heart rhythms, and the *cerebellum* which helps control movement.

THE TOLL OF MAJOR BRAIN AND NERVOUS SYSTEM DISEASES

Disease	*Total Cases*[a]	*Costs/Year*[a]
Eye Disease	80,000,000[b]	$ 16 billion
Hearing Loss	28,000,000	56 billion
Alzheimer's Disease	4,000,000	80 billion
Depression	3,500,000[c]	16 billion
Stroke	2,000,000	25 billion
Epilepsy	2,000,000	3 billion
Schizophrenia	1,110,000[c]	21 billion
Traumatic Head Injury	1,000,000	25 billion
Parkinson's Disease	500,000	2 billion
Traumatic Spinal Cord Injury	250,000	2 billion
Multiple Sclerosis	250,000	2 billion
Brain Tumors	62,000	325 million
Amyotrophic Lateral Sclerosis	30,000	300 million

[a] estimates.
[b] includes eye disorders exclusive of those requiring glasses.
[c] one-month prevalence.

Sources: National Institutes of Health, voluntary organizations.

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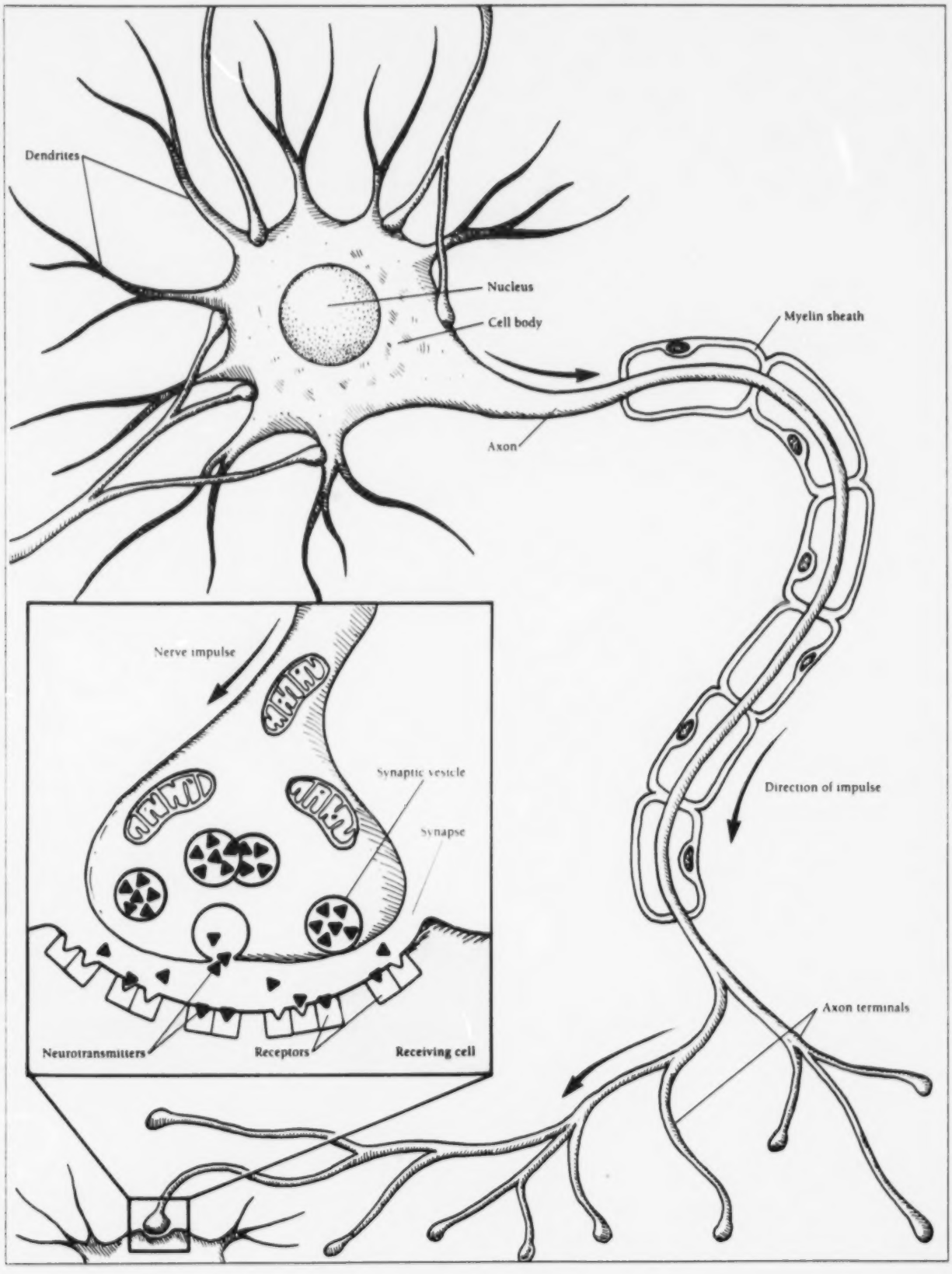

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THE NEURON

The neuron, or nerve cell, is the basic working unit of the brain. It is a specialized cell designed to transmit information to other neurons, muscle or gland cells. The brain is what it is because of the structural and functional properties of neurons.

A neuron consists of a cell body containing the nucleus and a conducting fiber, the axon, which may branch into smaller axons before terminating. Along its course and at the ends of its branches, the axon forms synapses (from the Greek words meaning to "clasp together") with nearby neurons. Other cell processes, termed dendrites (from the Greek word for the branches of a tree), extend from the neuron cell body. The dendrites and cell body are covered with synapses formed by the ends of axons of other neurons.

Neurons signal by transmitting electrical impulses along their axons which can range in length from a tiny fraction of an inch to three or more feet. Many axons are covered with layered insulating *myelin sheaths* made of specialized cells which speed the transmission of electrical signals along the axon.

Nerve impulses involve the opening and closing of *ion channels*, water filled molecular tunnels that pass through the cell membrane and allow charged atoms or small molecules to enter or leave the cell. The flow of ions across the cell membrane creates an electrical current that produces tiny voltage changes across the membrane. On reaching the ends of an axon, these voltage changes trigger the release of special chemicals, *neurotransmitters*, which relay the impulse to the next neuron. The ability of a neuron to fire depends on a small difference in electrical potential between the inside and outside of the cell. When a nerve impulse begins, a dramatic reversal occurs in this potential at one point on the cell's membrane. The change, called an *action potential*, then passes along the membrane of the axon at speeds up to several hundred miles an hour. In this way, a neuron may be able to fire impulses scores or even hundreds of times every second.

Neurotransmitters released at nerve endings act by binding to *receptor molecules* present on the surfaces of neurons. These receptors act as on and off switches for the next cell. Each receptor has a distinctly shaped part that exactly matches a particular chemical messenger. A neurotransmitter fits into this region in much the same way as a key fits an automobile ignition. And when it does, it alters the neuron's outer membrane and triggers a change, such as the contraction of a muscle or increased activity of an enzyme-producing cell.

Receptor molecules for neurotransmitters are different from *sensory receptor cells*. The skin for instance, contains many types of sensory receptor cells that respond to stimuli such as pressure, touch, heat, cold and hair movement. The ear contains a structure called the cochlea, which houses specialized receptors that respond to sound; another set responds to movements of the head, providing the sense of balance. Other specialized receptors are located in the eyes, nose and mouth.

Knowledge of neurotransmitters in the brain and the action of drugs on these chemicals — gained entirely through the study of animals — is one of the largest fields in neuroscience. Armed with this information, scientists hope to understand the circuits that may be responsible for disorders such as Alzheimer's disease and Parkinson's disease. Sorting out the various chemical circuits is also vital to understanding how the brain stores memories, why sex is such a powerful motivator and the biological basis of mental illness.

NEURON. A neuron fires by transmitting electrical signals along its *axons*. When they reach the end of the axons, the signals trigger the release of *neurotransmitters* which are stored in pouches called *synaptic vesicles*. Neurotransmitters bind to *receptor molecules*, which are present on the surfaces of adjacent neurons. This interaction relays the message to the next neuron. This point of contact is known as the *synapse*.

NEUROTRANSMITTERS

Acetylcholine • The first neurotransmitter to be identified more than 60 years ago, acetylcholine (ACh) is the standard by which all others are judged. ACh is released by neurons connected to skeletal muscles (causing them to contract) and by neurons that control the heart beat; it also transmits messages between neurons in the brain and

spinal cord. Interference with the action of ACh on skeletal muscles is the cause of *myasthenia gravis*, a disease characterized by easy fatigability and weakness of muscles.

ACh is formed at the axon terminals or synthesized in the cell body of the neuron and transported down the axon to the terminals. When an action potential arrives at the terminal, the calcium ion rushes in and ACh is released into the synapse and attaches to ACh receptors. In skeletal muscles, this opens sodium ion channels, causing the muscle to contract. ACh is then broken down and reused.

Much less is known about ACh in the brain. Recent discoveries suggest, however, that it may be critical for normal intellectual activities. Since ACh-releasing neurons are depleted in Alzheimer's patients, finding ways to restore this chemical is a major goal of current research.

Amino Acids • Certain amino acids are widely distributed in the brain and other body tissues but since they perform so many roles within cells, scientists disagree on how to distinguish their action as transmitters from other tasks.

The neurotransmitters *glutamate* and *aspartate* act as excitatory signals. *Glycine* and *gamma-amino butyric acid* (GABA) inhibit the firing of neurons. The activity of GABA is increased by benzodiazepine (Valium) and by anticonvulsant drugs. It has been suggested that people with Huntington's chorea have degeneration of GABA-producing neurons in the brain centers that coordinate movement.

ACTION OF NEUROTRANSMITTERS IN THE BRAIN PLAYS A VITAL ROLE IN KEY BODILY FUNCTIONS, RANGING FROM LEARNING AND MEMORY TO MOVEMENT AND EMOTION.

Glutamate or aspartate probably stimulate so-called *N-methyl-D-aspartate* (NMDA) receptors which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in a developing animal. The stimulation of NMDA receptors may promote beneficial changes in the brain, whereas overstimulation can cause nerve cell damage or death in neurological trauma and stroke.

Key questions remain about their precise structure, regulation, location and function. Unraveling these issues and developing drugs to block or encourage activity at NMDA receptors hold promise for improving brain function and treating neurological disorders. But this work is just at the beginning stage.

Catecholamines • *Dopamine* and *norepinephrine* are widely present in the brain and peripheral nervous system. Dopamine, which is present in three circuits in the brain, is thought to play a role in movement, regulating emotional responses and schizophrenia.

In one circuit, dopamine regulates the endocrine system. It directs the *hypothalamus* to manufacture hormones and hold them in the *pituitary gland* for release into the bloodstream, or triggers the discharge of hormones held in cells in the pituitary.

The dopamine circuit regulating movement has been directly related to disease. The brains of people with Parkinson's disease — which causes muscle tremors, rigidity and difficulty in moving — have practically no dopamine. Thus, medical scientists found that use of *levodopa*, a substance from which dopamine is manufactured, was a useful treatment for Parkinson's patients.

Another dopamine circuit is thought to be important for cognition and emotion; abnormalities in this system have been implicated in schizophrenia. Since drugs that block dopamine receptors in the brain are helpful in diminishing psychotic symptoms, learning more about dopamine is important to understanding this illness.

Nerve fibers containing norepinephrine are ubiquitous in the brain. Norepinephrine is secreted by the adrenal gland in response to stress or events that produce arousal. Deficiencies of this transmitter occur in patients with Alzheimer's and in those with Korsakoff's syndrome, a cognitive disorder associated with chronic alcoholism. Thus, researchers believe norepinephrine may play a role in learning and memory.

Serotonin • Present in many tissues, particularly blood platelets, the lining of the digestive tract and the brain, serotonin was first thought to be involved in high blood pressure because it is present in blood and induces a very powerful contraction of smooth muscles. In the brain, it has been implicated in states of consciousness, mood, depression and anxiety. Because serotonin seems to control the different switches affecting various emotional states, scientists believe these switches can be blocked by an *analog*, a chemical with a similar molecular structure. Researchers are actively looking for such chemicals.

Peptides • These chains of amino acids linked together have been studied as neurotransmitters only in recent years. Brain chemicals called *opioids* — many of which are peptides — range from acting like opium to kill pain to causing sleepiness. (Peptides differ from proteins which are much larger and more complex combinations of amino acids.) In 1973, scientists discovered receptors for opiates on neurons in several regions in the brain which suggested the brain must make substances very similar to opium. Shortly thereafter, scientists made

their first discovery of an opiate produced by the brain that resembles morphine, an opium derivative used medically to kill pain. They named it *enkephalin*, literally meaning "in the head." Subsequently, other opiates known as *endorphins* — from endogenous morphine — have been discovered.

The precise role of the opioids in the body is unclear. A plausible guess is that enkephalins are released by brain neurons in times of stress to minimize pain and enhance adaptive behavior. They may explain, for example, why a minor injury received during athletics is often not noticed until hours after it has occurred.

Opioids and their receptors are closely associated with pathways in the brain activated by painful or tissue-damaging stimuli. These signals are transmitted to the *central nervous system* — the brain and spinal cord — by small myelinated fibers and tiny unmyelinated or *C fibers*.

Scientists have recently discovered that some C fibers contain a chemical, *substance P*. While not yet proved, it seems reasonable to believe substance P is one of the chemicals released at the synapses the C fibers make in the spinal cord.

Hormones • After the nervous system, the endocrine system is the second great communication system of the body. It works through the pituitary which secretes hormones into the blood. As endorphins are released from the pituitary gland, they are almost by definition endocrine hormones. Hormones activate specific receptors in target organs that release other hormones into the blood that act on other tissues, the pituitary itself and the brain. This system is very important for the activation and control of basic behavioral activities such as sex, emotion, response to stress and the regulation of body functions such as growth, energy use and metabolism.

Hormones act by attaching to receptors on cells that are similar to neurotransmitter receptors; a specific hormone receptor will be activated only by a specific hormone. The entire system is under the control of the pituitary gland, located at the base of the brain. The pituitary, in turn, is controlled by the hypothalamus.

Actions of hormones show the brain to be a very malleable organ that responds to environmental signals. The brain contains receptors for thyroid hormone and for the six classes of steroid hormones — *estrogens, androgens, progestins, glucocorticoids, mineralocorticoids* and *vitamin D*. The receptors are found in selected populations of neurons and also in some *glial*, or support, cells. They bind to genetic material and regulate expression of genes in the cell nuclei.

In response to stress and changes in our biological clocks — such as day-and-night cycles and jet-lag — hormones are dumped into the blood and travel to the brain and other organs. In the brain, they alter the production of gene products that participate in synaptic neurotransmission as well as the structure of brain cells. As a result, the circuitry of the brain and its capacity for neurotransmission are changed over a time course of hours to days. In this way, the brain adjusts its performance and control of behavior in response to a changing environment.

Reproduction is a good example of a regular, cyclic process driven by circulating hormones: the hypothalamus produces *gonadotropin-releasing hormone*, a peptide that is a special hormone, which acts on cells in the pituitary. In both males and females, this causes two hormones — *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH) — to be released into the bloodstream. In males, these hormones are carried to receptors on cells in the testes where they release the male hormone testosterone into the bloodstream. In females, FSH and LH act on the ovaries where they cause the release of the female hormones estrogen and progesterone. In turn, the increased levels of testosterone in males and estrogen in females acts back on the hypothalamus and pituitary to decrease the release of FSH and LH. The increased levels also induce changes in cell structure and chemistry which lead to an increased capacity of the animal to engage in sexual behavior.

Intracellular Messengers

Recently recognized substances that trigger biochemical communication within the cell membrane, *second messengers* may be responsible for long-term changes in the nervous system. They convey the chemical message of a neurotransmitter (the first messenger) from the cell membrane to the cell's biochemical machinery. Second messengers take anywhere from a few milliseconds to minutes to transmit a message.

An example of the initial step in the activation of a second messenger system involves *adenosine triphosphate* (ATP), the chemical source of energy in cells. ATP is present throughout the cell. When the receptor molecule is activated by its chemical messenger or transmitter (the first messenger), it causes ATP to undergo a chemical reaction that produces another chemical, *cyclic adenosine monophosphate* (cAMP). The enzyme that induces this reaction is *adenyl cyclase*. cAMP can exert a variety of influences on the cell, ranging from changes in the membrane to changes in the activity of the genetic material in the nucleus, rather than acting as a messenger between one neuron and another. cAMP is called a second messenger because it acts after the first messenger, the transmitter chemical, has crossed the synaptic space and attached to a receptor.

Second messengers are also thought to play a role in the manufacture and release of neurotransmitters, intracellular movements, carbohydrate metabolism in the cerebrum — the largest part of the brain consisting of two hemispheres — and possibly processes of growth and development. Direct effects of these substances on the genetic material of cells may lead to long-term alterations of behavior such as memory.

Brain Development

From the single cell formed at conception, the first signs of the brain appear during the next three weeks when the human embryo grows to a length of about a tenth of an inch. An initial group of cells are connected into a hollow, elongated structure called the neural tube. At the front of this tube a swelling appears that eventually develops into the brain.

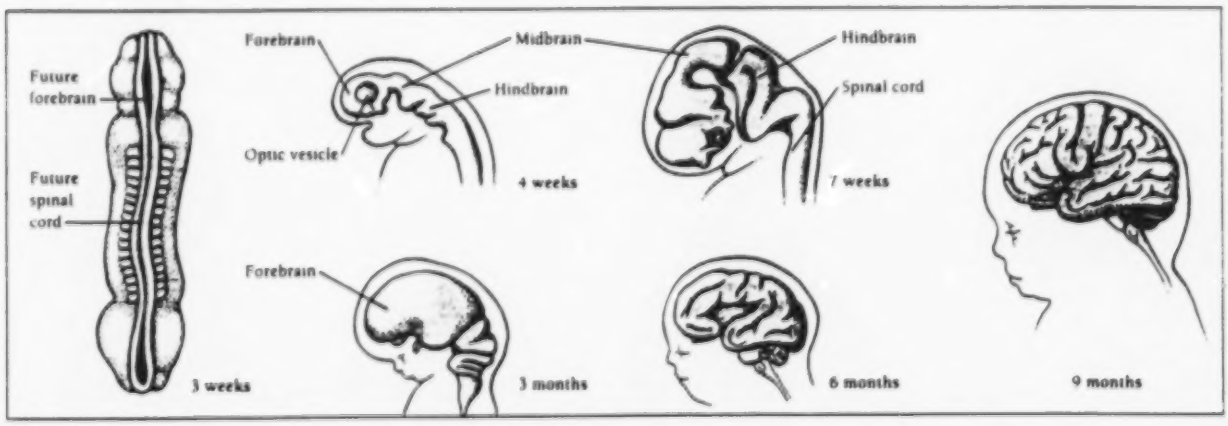
By five weeks, all the major brain regions are recognizable. Brain cells multiply very rapidly at two periods: age 15 to 20 weeks in the womb and again at a very low level at 25 weeks until about a year after birth. Eventually, the central nervous system develops into a network of billions of neurons that migrate to preordained places to form the major circuits of the brain and spinal cord. These cells are all generated before birth and no new ones are formed thereafter. In other words, we are born with virtually all neurons that will form the adult brain. If anything, neurons are overproduced and excess cells and processes are "pruned" over the course of development. This process is influenced by experience and by genetic programs.

All the neurons and many glial cells that will comprise the vital structures of the central nervous system are generated in germinal zones. They migrate to their final positions in nuclear groups and layered structures such as the cortex. As they migrate, they form transient contacts with other migrating elements but once they reach their ultimate locations, they begin to differentiate into specific cells with specific biochemical properties and connections.

Once cells have attained their ultimate residence, further development consists of enlargement, elaboration of axons and dendrites and finally the establishment of synapses with other cells. Humans, monkeys and rats experience a period of excess synapses (roughly 1½ years in humans and 2 to 4 months in monkeys) and the density of synapses decreases to adult levels at the time of puberty.

The basic principles of brain development are beginning to be known and appear to be similar across all mammals. During the next few years, scientists should be able to capitalize on these principles to enrich the understanding of developmental disorders caused by defects in these regulatory processes.

Brain Development. The human brain and nervous system begin at three weeks gestation as the closing *neural tube* (left). By four weeks, major regions of the human brain can be recognized in primitive form, including the *forebrain, midbrain, hindbrain* and *optic vesicle* (from which the eye develops). Convolutions (irregular ridges) appear during the middle of pregnancy and are clearly seen by six months. Because the fully developed human brain contains 100 billion neurons and no more are added after birth, they must be generated at a rate of more than a quarter of a million per minute during development.



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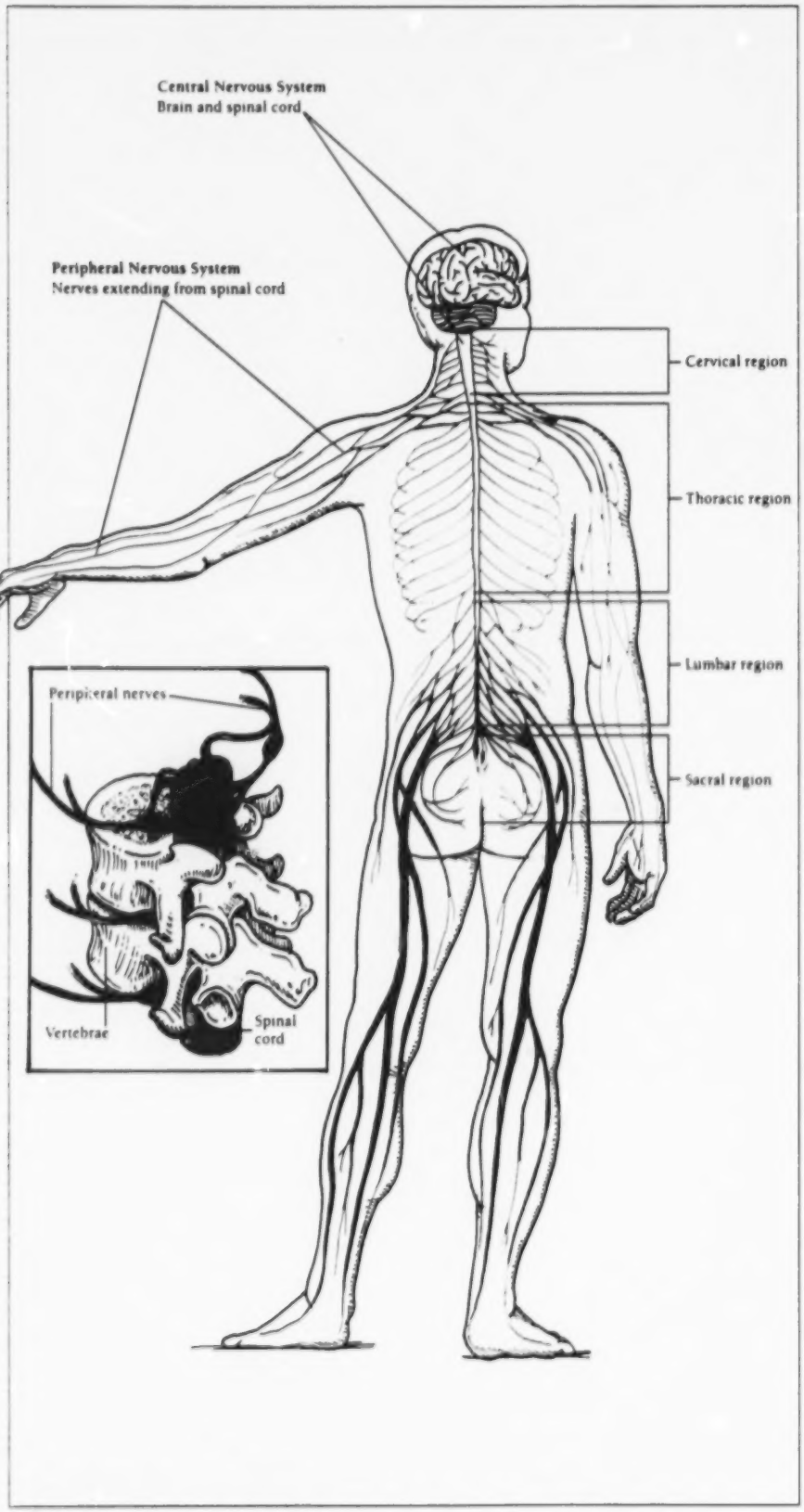

SPINAL CORD AND NERVES. The *central nervous system* (CNS) consists of the brain and spinal cord. The brain sends nerve signals to the spinal cord which relays them to specific parts of the body through peripheral nerves, known as the *peripheral nervous system* (PNS). Peripheral nerves in the *cervical region* serve the neck and arms; those in the *thoracic region* serve the trunk; those in the *lumbar region* serve the legs; and those in the *sacral region* serve the bowels and bladder. The PNS consists of the *somatic nervous system* which connects voluntary skeletal muscles with cells specialized to respond to sensations such as touch and pain. The *autonomic nervous system* is made up of neurons connecting the CNS with internal organs. It is divided into the *sympathetic nervous system*, which mobilizes energy and resources during times of stress and arousal, and the *parasympathetic nervous system*, which conserves energy and resources during relaxed states.

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Sensation and Perception

Vision. This wonderful sense allows us to perceive form, color, depth and movement in the world around us, from the genius of Michelangelo's Sistine Chapel ceiling to mist-filled vistas of a mountain range. Vision is one of the most delicate and complicated of all the senses. It is also the most studied. More is known about vision than any other vertebrate sensory system, with most of the information derived from studies of monkeys and cats.

Primates, including humans, have well-developed vision using two eyes. Visual signals pass from each eye along the million or so fibers of the optic nerve to the optic chiasm where some nerve fibers cross over, so both sides of the brain receive signals from both eyes. Consequently, the left halves of both retinas project to the left visual cortex and the right halves project to the right visual cortex.

The effect is that the left half of the scene you are looking at registers in your right hemisphere. Conversely, the right half of the scene you are looking at registers in your left hemisphere. A similar arrangement applies to movement and touch: each half of the cerebrum is responsible for the opposite half of the body.

Scientists know much about the way cells code visual information in the retina, *lateral geniculate nucleus* — an intermediate point between the retina and visual cortex — and *visual cortex*. These studies give us the best knowledge so far about how the brain analyzes and processes information.

The retina contains three stages of neurons. The first, the layer of *rods* and *cones*, sends its signals to the middle layer which relays signals to the third layer. Nerve fibers from the third layer assemble to form the *optic nerve*. Each cell in the middle or third layer receives input from many cells in the previous layer. Any cell in the third layer thus receives signals (via the middle layer) from a cluster of many thousands of rods and cones that cover about a square millimeter. This region is called the *receptive field* of the third-layer cell.

About 40 years ago, scientists discovered that the receptive field of such a cell is activated when light hits a tiny region in its receptive field center and is inhibited when light hits the part of the receptive field surrounding the center. If light covers the entire receptive field, the cell reacts only weakly and perhaps not at all.

Thus, the visual process begins with a comparison of the amount of light striking any small region of the retina with the amount of light around it.

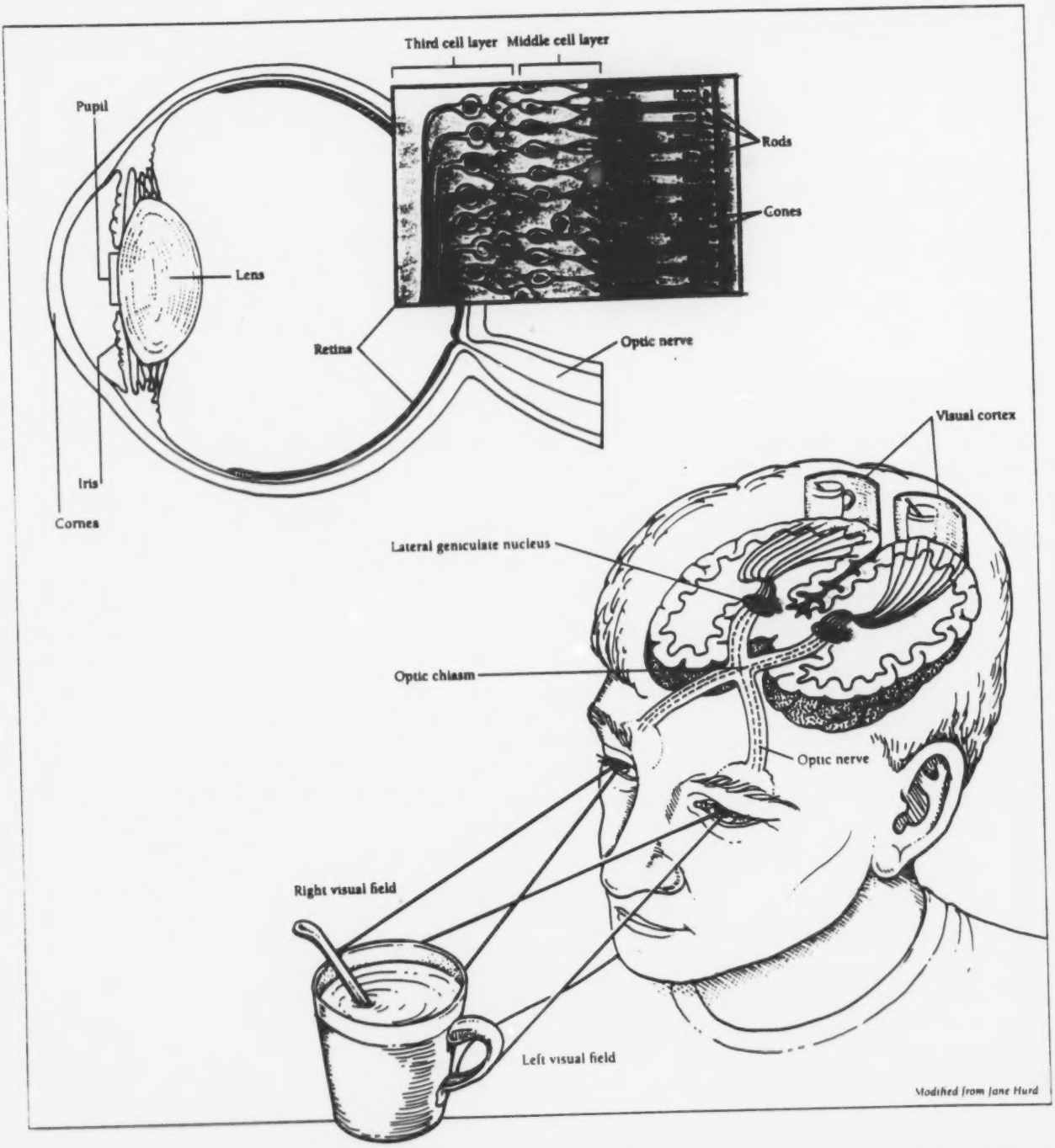
Located in the *occipital lobe*, the *primary visual cortex* — two millimeters thick and densely packed with cells in many layers — receives messages from the lateral geniculate. In the middle layer, where these messages first arrive, scientists found patterns of responsiveness similar to those observed in the cells of the retina and lateral geniculate. Cells above and below this layer responded differently. They preferred stimuli in the shape of bars or edges. Further studies showed that different cells preferred edges at particular angles, edges that moved or movement in a particular direction.

While the process is not yet completely understood, recent findings suggest that visual signals are fed into at least three separate processing systems. One system appears to process information about shape; a second, color; and a third, movement, location and spatial organization. These findings of separate processing systems come from monkey anatomical and physiological data. They are verified by human psychological studies showing that the perception of movement, depth, perspective, the relative size of objects, the relative movement of objects and shading and gradations in texture all depend primarily on contrasts in light intensity rather than color.

Why movement and depth perception should be carried by only one processing system may be explained by a school of thought called Gestalt psychology. Perception requires various elements to be organized so that related ones are grouped together. This stems from the brain's ability to group the parts of an image together and also to separate images from one another and from those in the background.

How do all these systems produce the solid images you see? By extracting biologically relevant information at each stage and associating firing patterns with past experience.

Vision studies have also led to better treatment for visual disorders. Information from research in cats and



VISION. The *cornea* and *lens* help produce a clear image of the visual world on the *retina*, the sheet of photoreceptors and neurons lining the back of the eye. As in a camera, the image on the retina is reversed: objects to the right of center project images to the left part of the retina and vice versa. The eye's 125 million visual receptors — *rods* and *cones* — turn light into electrical signals. Rods are most sensitive to dim light and do not convey the sense of color; cones work in bright light and are responsible for acute detail, black and white and color vision. The human eye contains three types of cones that are sensitive to red, green and blue but in combination convey information about all visible colors. Rods and cones connect with a middle cell layer and third cell layer (see inset). Light passes through these two layers before reaching the rods and cones. The two layers then receive signals from the rods and cones before transmitting the signals on to the *optic nerve*, *optic chiasm*, *lateral geniculate nucleus* and finally, the *visual cortex*.

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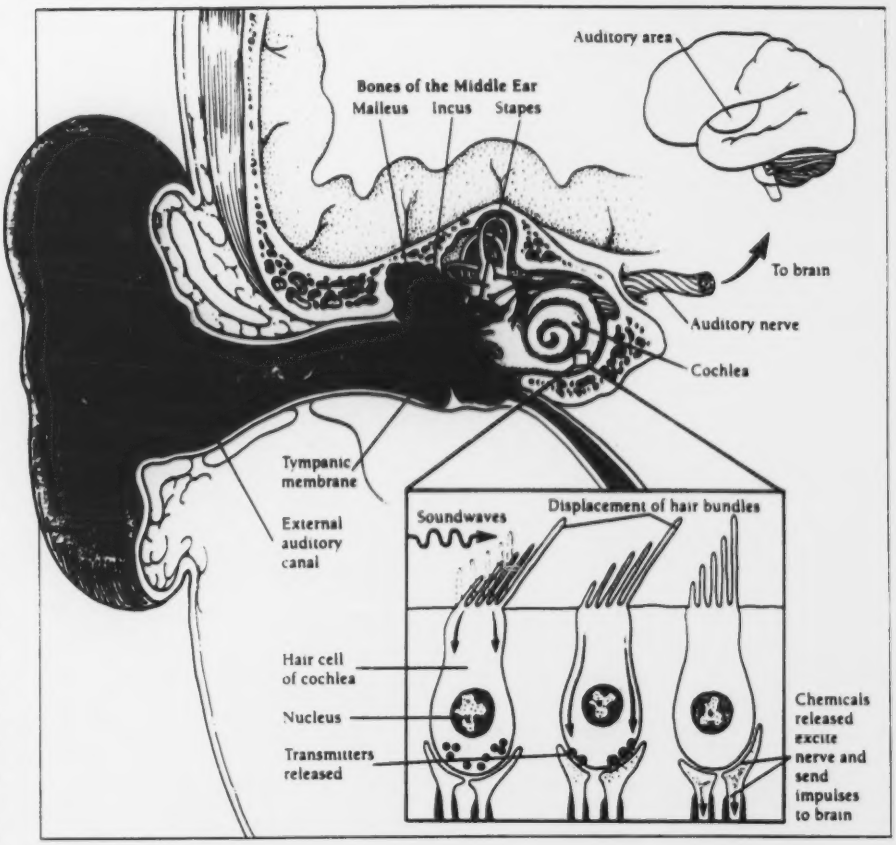

HEARING. From the chirping of crickets to the roar of a rocket engine, almost all of the thousands of single tones processed by the human ear are heard by a mechanism known as *air conduction*. In this process, sound waves are first funneled through the externally visible part of the ear, the *pinna* (or external ear) and the *external auditory canal* to the *tympanic membrane* (eardrum) which vibrates at different speeds. The *malleus* (hammer) which is attached to the tympanic membrane, transmits the vibrations to the *incus* (anvil). The vibrations are then passed on to the *stapes* (stirrup) and *oval window* which passes them to the inner ear. In the inner ear, the fluid-filled spiral passage of the *cochlea* contains cells whose microscopic, hair-like projections respond to the vibrations produced by sound. The hair cells, in turn, excite the 28,000 fibers of the auditory nerve that end in the medulla in the brain. Auditory information flows via the thalamus to the *temporal gyrus*, the part of the cerebral cortex involved in receiving and perceiving sound.

monkeys has improved the therapy for *strabismus*, or *squint*, a term for cross-eye or wall-eye. Children with strabismus initially have good vision in each eye. But because they cannot fuse the images in the two eyes, they tend to favor using one eye and often lose useful vision in the other eye.

Vision can be restored but only during infancy or early childhood. Beyond the age of six or so, the blindness becomes permanent. But until about a decade ago, ophthalmologists waited until children reached the age of four before operating to align the eyes or prescribing exercises or an eye patch. Now strabismus is corrected very early in life — well before age four — when normal vision can still be restored.

HEARING

Often considered the most important sense for humans, hearing allows us to communicate with each other by receiving sounds and interpreting speech. It also gives us information vital to survival, such as the sound of an oncoming train which tells us to stay clear of the railroad track.

Our hearing system distinguishes several qualities in the signal it detects, just like the visual system. Pitch — high or low — is determined by the frequency of sound waves. Loudness is a measure of intensity. Timbre is the mixture of frequencies.

However, our hearing system does not blend different sounds, as the visual system does when two different wavelengths of light are mixed to produce color. We can follow the separate melodic lines of several instruments as we listen to an orchestra or rock band. The brain's analysis of auditory information follows a pattern similar to that of the visual system. Adjacent neurons respond to tones that are only a note apart. Some neurons respond to only a small range of frequencies; others react to a wide range; some react only to the beginning of a sound; others only to the end.

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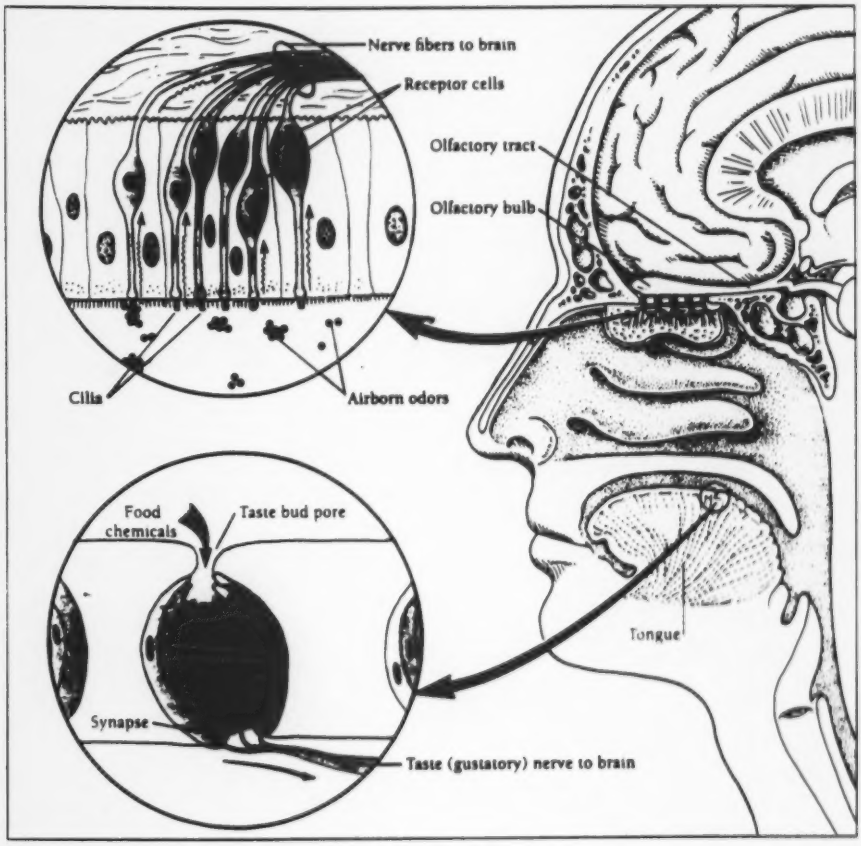

Speech sounds, however, may be processed differently than others. Our auditory system processes all the signals it receives in the same way until they reach the primary auditory cortex in the *temporal lobe* of the brain. When speech sound is perceived, the neural signal is funneled to the left hemisphere for processing in language centers.

Smell and Taste

Although different, these two sensory experiences are intimately entwined. Smell and taste are separate senses with their own receptor organs. However, these two senses act together to allow us to distinguish thousands of different flavors. Alone, taste is a relatively primitive sense, able to distinguish only between sweet, salty, sour and bitter. This combination explains why loss of the sense of smell also apparently causes a serious reduction in taste. Like other sensory systems, the smell process is probably based on a physical fit between the odor molecules and receptor sites. Receptors on some cells, for example, may react only with molecules of garlic, others only with molecules of bleach. The molecules must dissolve in the mucous membrane lining the roof of the nose before they can stimulate the receptors.

Touch and Pain

Touch is the sense by which we determine the characteristics of objects: size, shape and texture. We do this through touch receptors in the skin. In hairy skin areas, some receptors consist of webs of sensory neuron endings wrapped around the hair bulbs. They are triggered if the hairs are moved. Other receptors are more common in non-hairy areas, such as lips and fingertips and consist of neuron endings that may be free or surrounded by bulblike structures.

Signals from touch receptors pass through sensory nerves to the spinal cord,

Smell and Taste. Specialized smell receptors are located in a small patch of mucous membrane lining the roof of the nose. Axons of these cells pass through perforations in the overlying bone and enter two elongated *olfactory bulbs* lying on top of the bone. The receptor cell bodies are swollen at their lower ends and attached to several hair-like *cilia* containing the receptor sites stimulated by odors carried by airborne molecules. Impulses created by this stimulation pass by olfactory nerve pathways to smell centers located in the frontal lobe and limbic system of the brain.

Tastes are detected by special structures, *taste buds*, of which every human has some 10,000. Taste buds are embedded within *papillae* (protuberances) mainly on the tongue, with a few in the back of the mouth and on the palate. Each taste bud consists of about 100 receptors that respond to the four types of stimuli — sweet, salty, sour and bitter — from which all tastes are formed. A substance is tasted when chemicals in foods dissolve in saliva and enter the pores on the tongue and come in contact with taste buds. Here they stimulate hairs projecting from the receptor cells and cause signals to be sent from the cells, via synapses, to cranial nerves and taste centers in the brain.

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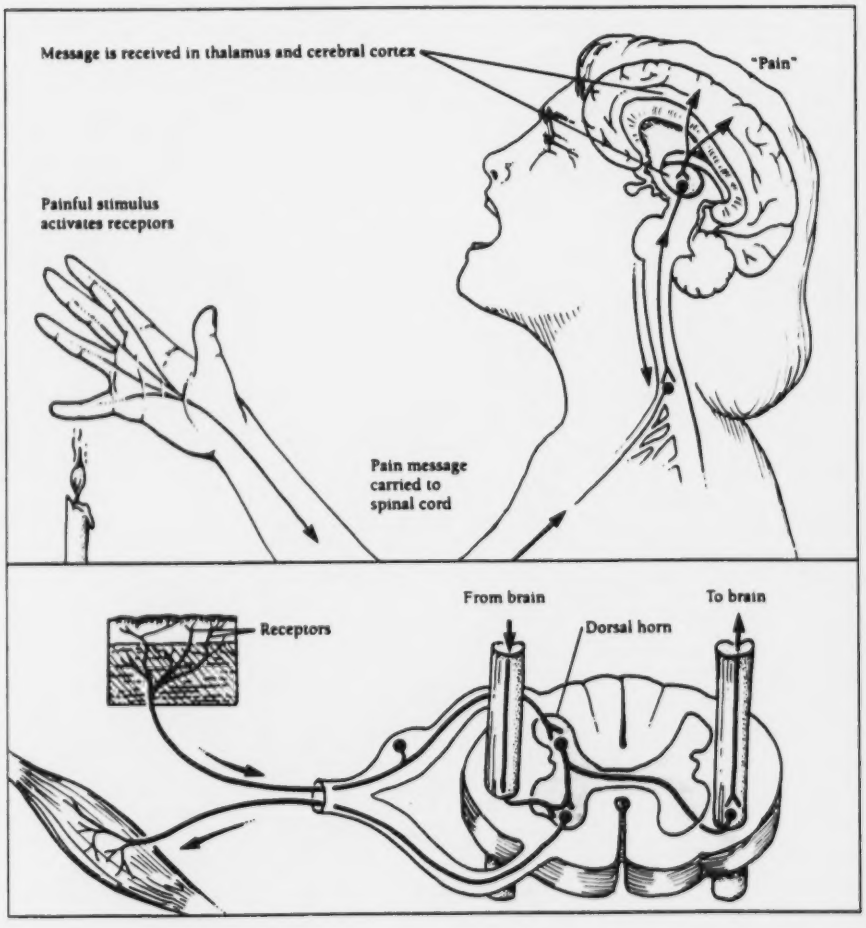
then to the *thalamus* and *sensory cortex* in the brain. Sensations perceived at certain points within these regions correspond to the parts of the body from which the signals originated. Larger areas of the cortex are devoted to sensations from the hands and lips than from less sensitive parts.

Different areas of the body vary in their sensitivity to touch discrimination and painful stimuli according to the number and distribution of receptors. The cornea is several hundred times more sensitive to painful stimuli than are the soles of the feet. The fingertips are good at touch discrimination but the chest and back are less sensitive.

Pain was recently thought to be like a simple message sent over a telegraph wire: neurons sent electrical impulses from the site of injury to the brain. From recent studies of animals, scientists now know that the process is much more complicated. While the total picture is not yet clear, scientists believe that perceiving and responding to pain involves dozens of chemical and electrical processes.

At the point of injury, special receptors respond to tissue-damaging stimuli. Injury results in the release of numerous chemicals at the site of damage and inflammation. One chemical, *prostaglandin*, enhances the sensitivity of receptors to tissue-damaging stimuli and ultimately can result in more intense pain sensations. The three major families of opioids identified in the brain — enkephalins, endorphins and dynorphins — originate from three precursor proteins coded by three different genes. They act at multiple opioid receptors in the brain. This knowledge has led to new treatments for pain: opiate-like drugs injected into the space above the spinal cord provide long-lasting pain relief.



PAIN. Messages about tissue damage are picked up by receptors and transmitted to the spinal cord via small myelinated and unmyelinated fibers. From the spinal cord, the impulses are carried to the brainstem, thalamus and cerebral cortex, and ultimately perceived as pain. These messages are suppressed by a system of neurons that originate in the gray matter in the brainstem of the midbrain. This *descending system* sends messages to the dorsal horn of the spinal cord where it suppresses the transmission of tissue damage signals to the higher brain centers. Some of these descending systems utilize naturally occurring chemicals similar to opioids.

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Learning and Memory

A patient known by his initials, H.M., lives almost entirely in the present. Since the time after surgery to remove structures in the medial area of the temporal lobe of his brain to relieve epilepsy, he can remember events for only a few minutes. Talk with him for a while and then leave the room. When you return he has no recollection of ever having seen you before.

Parts of the temporal lobe — the hippocampus and the medial temporal area — seem to play a role in the process of memory consolidation: changes that go on as the brain organizes and restructures information that may become a part of permanent memory. The fact that H.M. retains memories for events preceeding his surgery is evidence the medial temporal area is not the site of permanent storage but that it plays a role in the formation of new memories.

The hippocampus and medial temporal region are connected with widespread areas of the cerebral cortex, especially the vast association regions responsible for thinking and linguistic processes. Whereas the medial temporal areas are important for consolidation of new learning, cortical areas may be more important for the storage of knowledge (e.g., vocabulary) and for how it is utilized in everyday situations.

Working memory, a type of transient memory that enables us to retain what someone has said just long enough to reply, depends on the *prefrontal cortex*. Researchers have found that certain neurons in this area are strongly influenced by dopamine, norepinephrine and other neurotransmitters such as acetylcholine. Dysfunction of these systems may be responsible for memory loss in several disorders, including Alzheimer's disease.

While much is unknown about learning and memory, scientists can recognize certain pieces of the process. For example, the brain appears to process different kinds of information in separate ways and to store it differently. *Procedural knowledge* is knowledge of how to do something as is expressed in skilled behavior. *Declarative knowledge* provides an explicit, consciously accessible record of individual previous experiences and a sense of familiarity about those experiences. Declarative knowledge requires processing in the medial temporal region and parts of the thalamus, while procedural knowledge does not.

An important factor that influences what is stored and can be retrieved from memory is whether the action is followed by rewarding or punishing consequences. This is a very important principle in determining what behaviors an organism will learn and remember.

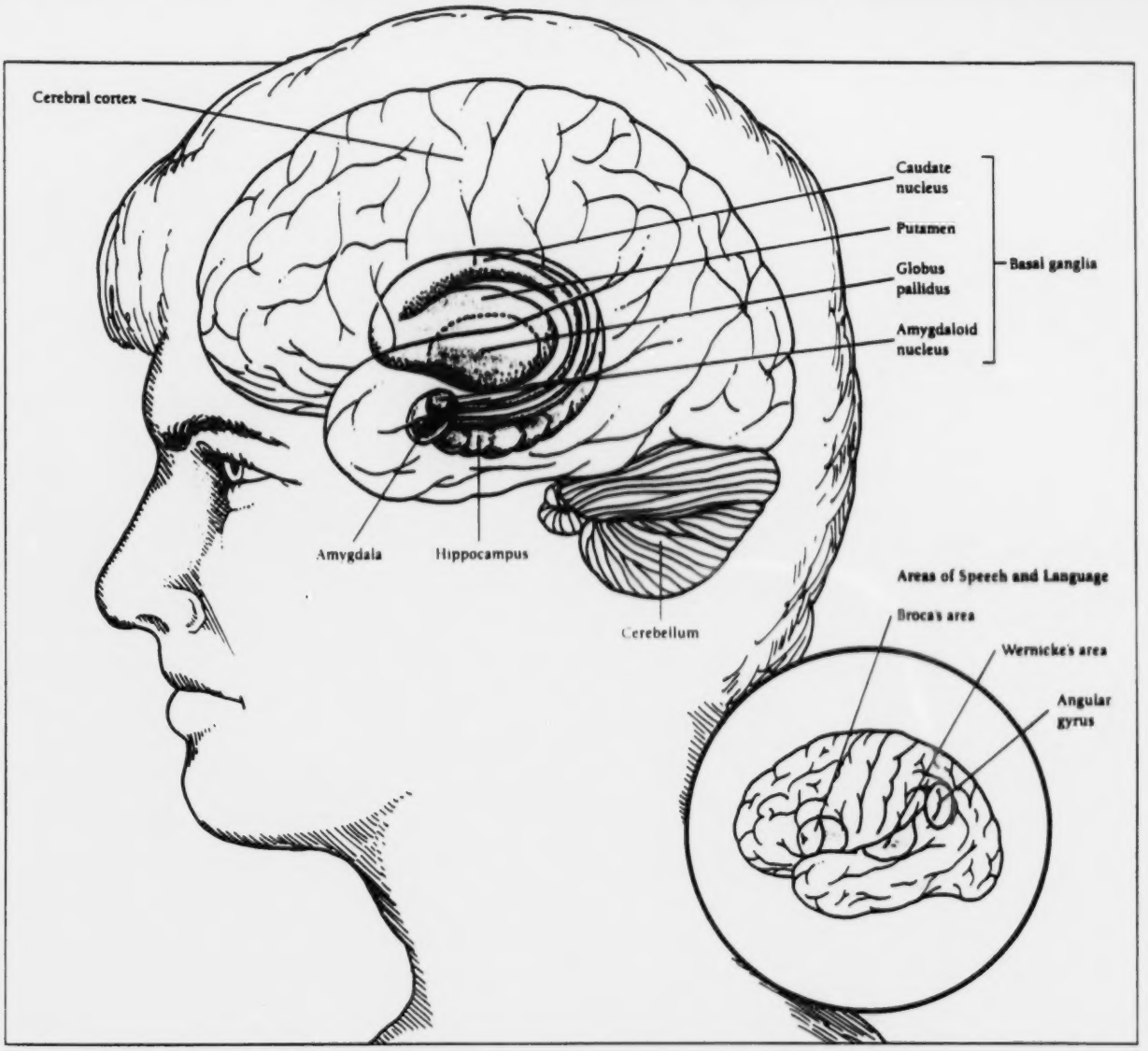
How exactly does memory occur? After years of study, there is much support for the idea that some forms of memory involve a persistent change in the relationship between neurons. In animal studies, scientists have found that this occurs either through actual structural modification or through stable biochemical events within neurons that change the strength of signals neurons send to their neighbors. For example, researchers can correlate specific chemical and structural changes in cells involved in several simple forms of behavioral change exhibited by the sea slug *Aplysia* and other invertebrate organisms.

Another important model for the study of memory is the phenomenon of *long-term potentiation* (LTP), a long-lasting increase in the strength of a synaptic response following stimulation. LTP occurs prominently in the hippocampus. Studies of rats suggest that memory is stored by changes in synaptic strength at contacts involving NMDA receptors. What makes memories specific to a particular event must depend largely on which neuronal connections are altered and on the architecture of the specific networks in which alterations occur.

Scientists believe that no single center in the brain stores memory. It is preserved in the set of particular cortical systems involved in the processing of specific sensory systems, such as vision and hearing. In short, each part of the brain contributes differently to memory.

One of the most prominent intellectual activities dependent on memory is language. Scientists have learned about this feature of the brain from studies of patients who have lost speech and language due to stroke, and from *positron emission tomography* (PET) scans of normal people.

The underlying structure of speech is thought to arise in a portion of the left hemisphere of the brain, *Wernicke's area*. The temporal lobe is connected with



LEARNING AND MEMORY, SPEECH AND LANGUAGE. Structures believed to be important for various kinds of learning and memory include the *cerebral cortex*, *amygdala*, *hippocampus*, *cerebellum* and *basal ganglia*. Areas of the left hemisphere, inset, are known to be active in speech and lauguage. The form and meaning of an utterance is believed to arise in *Wernicke's area* and then *Broca's area*, which is related to vocalization. Wernicke's area is also important for language comprehension.

Broca's area in the frontal lobe where it creates a program for vocal expression. This program is then transmitted to a nearby area of the motor cortex that activates the mouth, tongue and larynx.

The neural basis of language is not yet understood. Scientists believe that when we hear a word, the sound is initially received in the primary auditory cortex and then passes through Wernicke's area if it is to be understood as a verbal message. When we read a word, the information is transmitted from the primary visual cortex to the *angular gyrus* where the message is somehow matched with the sounds of the words when spoken. The auditory form of the word is then processed for comprehension in Wernicke's area as if the word had been heard.

Writing in response to an oral instruction requires information to be passed along the same pathways in the opposite direction: from the auditory cortex to Wernicke's area to the angular gyrus.

Using PET scans, scientists have recently shown that increasingly complex language tasks performed by normal people activated neither Wernicke's area nor the angular gyrus. These results appear to offer direct confirmation of a reading route that does not involve recoding of the visual stimulus before semantic processing. Unfamiliar words appear to be recoded into sound first, whereas familiar words tend to use only a visual route.

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MOVEMENT

From the stands, we all marvel at the perfectly placed serves of professional tennis players and lightning-fast double plays by big league baseball teams. But in fact, every one of us in our daily lives performs highly skilled movements, such as walking upright, speaking and writing that are no less remarkable. A finely tuned central nervous system controls the action of hundreds of muscles to accomplish these everyday marvels.

Understanding how the nervous system performs this trick starts with muscles. Most muscles attach to points on the skeleton that cross one or more joints. Activation of a given muscle, the *agonist*, can open or close the joints it spans or act to stiffen them, depending on the forces acting on those joints from the environment or from other muscles that oppose the agonist, the *antagonist*. Relatively few muscles act on soft tissue.

A muscle consists of thousands of individual fibers controlled by *alpha motor neurons* in the brain or spinal cord. A single alpha neuron can control hundreds of muscle fibers, forming a *motor unit*.

These motor neurons are the critical link between the brain and muscles. When they die, as occurs for still unknown reasons in *amyotrophic lateral sclerosis* (ALS), also known as Lou Gehrig's disease, a person is no longer able to move. Impulses in motor neurons release acetylcholine (ACh) which acts on receptor molecules in the muscle fibers, causing them to contract. Myasthenia gravis, which results from interference with the action of ACh, can now be helped with drugs that enhance ACh responses.

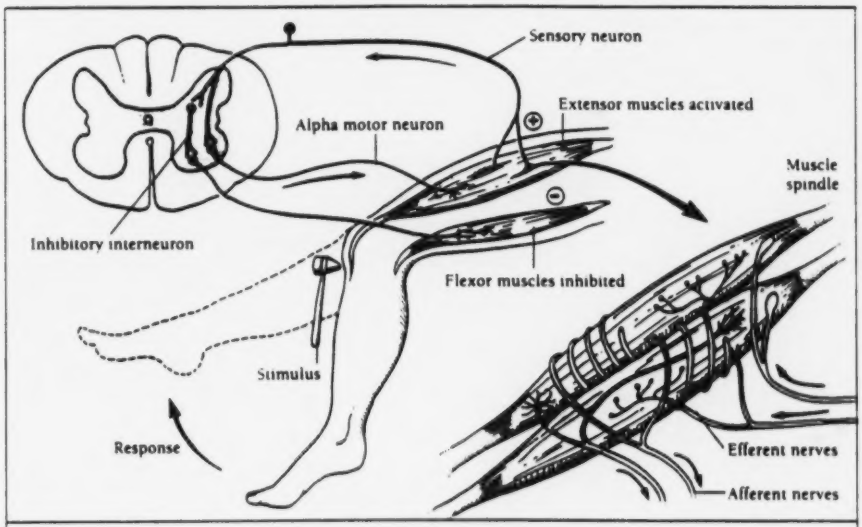
The simplest movements are reflexes, fixed muscle responses to particular stimuli, that have been studied extensively in cats and monkeys during the last century. Sensory stretch receptors — called *muscle spindles* located in most muscles — send information about muscle length directly to alpha motor neurons. Sudden muscle stretch (such as when a doctor taps a muscle tendon to test your reflexes) sends a barrage of impulses into the spinal cord along the muscle spindle sensory fibers. This in turn activates motor neurons in the stretched muscle, causing contraction which is called the stretch reflex. The same sensory stimulus causes inactivation, or inhibition, in the motor neurons of the antagonist muscles through connecting neurons, called *inhibitory interneurons*, within the spinal cord.

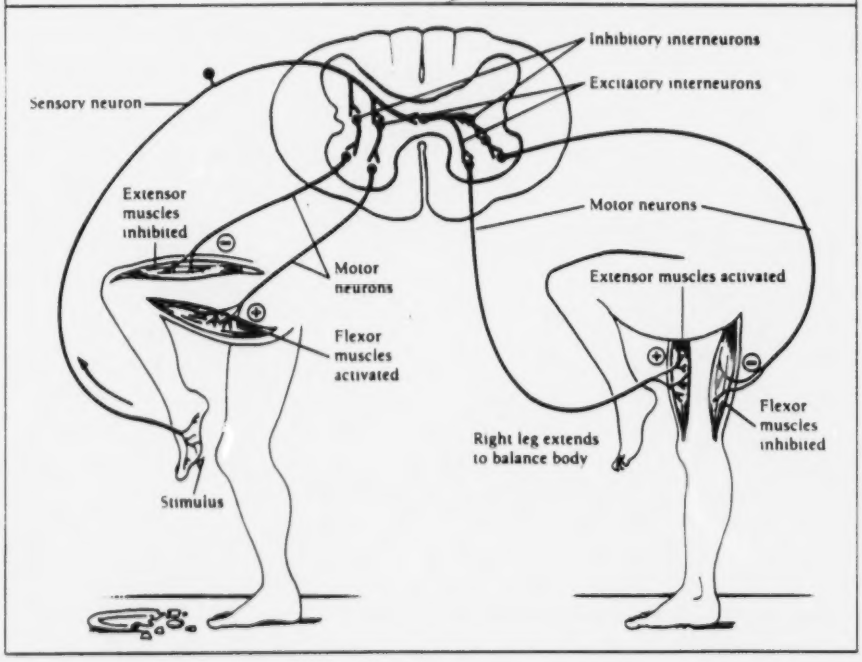
The sensitivity of muscle spindle organs is controlled by the brain through a separate set of *gamma motor neurons* which allow the brain to fine-tune the system for different movement tasks. Other muscle sense organs signal muscle force that affects motor neurons through separate sets of spinal interneurons. This complex system responds differently for tasks that require precise control of position (holding a full teacup), as opposed to those that require rapid, strong movement (throwing a ball). You can experience these changes in motor strategy when you compare walking down a staircase in the dark with the same task while the stairs are illuminated.

It seems likely that the systems of spinal interneurons involved in reflexes also participate in controlling the alternating action of the legs during normal walking. In fact, the basic patterns of muscle activation that produce coordinated walking can be generated in four-footed animals within the spinal cord itself. These spinal mechanisms, which evolved in primitive vertebrates, are still present in the human spinal cord.

The most complex movements that we perform, including voluntary acts requiring conscious planning, involve control of the spinal mechanisms by the brain. Scientists are only beginning to understand the complex interactions that take place between different brain regions during voluntary movements, mostly through careful experiments on animals. One major area is the *motor cortex*, located on the side of the frontal lobe of the cerebrum, which exerts powerful control of the spinal cord interneurons and has direct control of some motor neurons in monkeys and humans. Some neurons in the motor cortex appear to specify the coordinated action of many muscles to produce organized movement of the limb to a particular place in space.

In addition to the motor cortex, movement control involves the interaction of many other regions, including the *basal ganglia* and thalamus, the *cerebellum* and a large number of neuron groups located within the midbrain and brainstem — regions connecting cerebral hemispheres with the spinal cord.





MOVEMENT. The *stretch reflex* (above) occurs when a doctor taps a muscle tendon to test your reflexes. This sends a barrage of impulses into the spinal cord along the muscle spindle sensory fibers, activating motor neurons in the stretched muscle to cause contraction (stretch reflex). The same sensory stimulus causes inactivation, or inhibition, in the motor neurons of the antagonist muscles through connecting neurons, called *inhibitory interneurons*, within the spinal cord. *Afferent nerves* carry messages from sense organs to the spinal cord; *efferent* nerves carry motor commands from the spinal cord to muscles. *Flexion withdrawal* (below) can occur when your bare foot encounters a sharp object. Your leg is immediately lifted (flexion) from the source of potential injury but the opposite leg responds with increased extension in order to maintain your balance. The latter event is called the *crossed extension reflex*. These responses occur very rapidly and without your attention because they are built into systems of interneurons within the spinal cord itself.

Scientists know that the basal ganglia and thalamus have widespread connections with sensory and motor areas of the cerebral cortex. Damage to these areas, which depend on dopamine, can cause serious movement disorders such as Parkinson's disease. Strategies to replace dopamine function are under study.

The cerebellum is critically involved in the control of all skilled movements. Loss of cerebellar function leads to poor coordination of muscle control and disorders of balance. The cerebellum receives direct and powerful sensory information from muscle receptors and from the sense organs of the inner ear that signal head position and movement, as well as signals from the cerebral cortex. It apparently acts to integrate all this information to ensure smooth coordination of muscle action, enabling us to perform skilled movements more or less automatically. There is evidence that, as we learn to walk, speak, or play the violin or piano, the necessary detailed control information is stored within the cerebellum where it can be called upon by commands from the cerebral cortex.

PARKINSON'S DISEASE. A brain disorder mostly of the elderly, Parkinson's is characterized by trembling, rigid posture, slow movements and a shuffling, unbalanced walk. It results from the degeneration of or damage to dopamine-containing neurons that originate in the substantia nigra of the brain and project into the basal ganglia. But the precise cause for Parkinson's is unknown and until recently it had no treatment. During the late 1950s, scientists associated the loss of dopamine with Parkinson's. They then found that levodopa improves the symptoms of most Parkinson's patients.

To reduce gastrointestinal side effects, levodopa is usually combined with the drug *carbidopa*. But the beneficial effects of levodopa gradually wear off, requiring the use of a combination of drugs including *bromocriptine*, *pergolide* and *amantadine*. The drug *deprenyl* may slow the progression of the disease. For some patients, an operation on the brain may reduce tremor and rigidity but better approaches are needed.

Recently, scientists successfully reduced Parkinson's-like symptoms in rats by injecting skin cells that have been genetically engineered to produce dopamine in the basal ganglia. Researchers have also transplanted adrenal gland and fetal brain tissue, both of which produce dopamine, into the brains of Parkinson's patients. However, much basic research must be completed before this strategy becomes useful for most patients.

Researchers are now working with an animal model of Parkinson's, monkeys injected with a substance called MPTP, which has opened the doors to new approaches to tissue implants and other therapies.

PAIN

If there is a universal experience, pain is it. Each year, more than 97 million Americans suffer chronic, debilitating headaches, a bout with a bad back or the pain of arthritis — all at a total cost of some $80 billion. But it need not be that way. New discoveries about how chemicals in the body transmit and intercept pain have paved the way for new treatments for both chronic and acute pain.

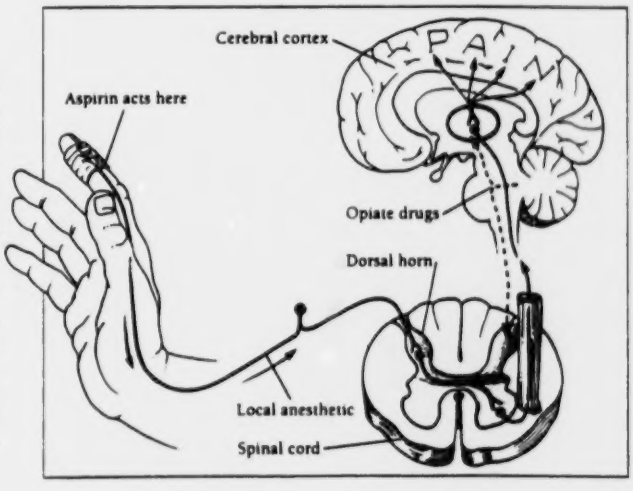
Until the middle of the 19th century, pain relief during surgery relied on natural substances such as opium, alcohol and cannabis. All were inadequate and short-lived. Not until 1846 did doctors discover the anesthetic properties of ether, first in animals and then in humans. Soon afterward, the usefulness of chloroform and nitrous oxide became known and heralded a new era in surgery.

The dozens of drugs used today during surgery abolish pain, relax muscles and induce unconsciousness. Other agents reverse these effects after an operation.

Local anesthesia is used in a limited area of a person's body to prevent pain during examinations, diagnostic procedures, treatments and surgical operations. The most famous of these agents, which temporarily interrupt the action of pain-carrying nerve fibers, is *novocaine*. Until recently, novocaine was used as a local anesthetic by dentists but *lidocaine* is more popular today.

Analgesia produces loss of pain sensation without loss

HOW PAIN KILLERS WORK. At the site of injury, the body produces *prostaglandins* which increase pain sensitivity. Some analgesics, such as aspirin, prevent the production of prostaglandins. Acetaminophen is believed to block pain impulses in the brain itself. Local anesthetics intercept pain signals traveling up the nerve. Opiate drugs prevent the transfer of pain signals from the spinal cord to the brain.



of sensitivity to touch. The two main types of analgesics are *non-opioids* (aspirin or acetaminophen) and *opioids* (morphine). Non-opioid analgesics are useful for treating mild or moderate pain such as headache or toothache. More severe pain can be treated by combining a mild opioid such as codeine with aspirin. The most potent pain-killers are used only when other preparations are ineffective.

Insights into the body's endorphin-mediated pain-control system have led to the use of injections of morphine, endorphins and other opioids into the space above the spinal cord without causing paralysis, numbness or other severe side effects. This technique came about through experiments with rats that first showed that injecting opiates into the space above the spinal cord could produce profound pain control. In humans, a single injection of morphine reduces pain for more than 24 hours, whereas the same dose given by mouth provides relief for only a few hours. This technique is now commonly used in humans to treat pain after surgery.

Epilepsy

A chronic neurological disorder resulting from sudden, disorderly discharges of energy by brain cells, epilepsy is marked by recurrent seizures that temporarily alter one or more brain functions.

It is a disorder that frequently starts in childhood or adolescence but many people outgrow it and no longer need medication. Epilepsy can result from a wide variety of diseases or injuries (including head injury), birth trauma, brain infection (such as meningitis or encephalitis), brain tumors, stroke, drug intoxication, drug or alcohol withdrawal states and metabolic disorders. But in 75 percent of cases the cause cannot be identified.

The drug *phenytoin*, first synthesized in 1908, sat on a pharmaceutical house shelf unused for 30 years until researchers, who were screening many agents in cats, found it to have anti-convulsive effects. Phenytoin was immediately used in humans and provided relief from epilepsy. The drug was a major advance in the treatment of epilepsy because it illustrated that anti-epileptic medications need not cause sedation (as does *phenobarbital*) and encouraged the search for other drugs.

Today several agents can prevent seizures. One of these drugs, *valproate*, was discovered accidently when it was used during the early 1960s to speed the absorption of other drugs being screened in mice models of epilepsy.

In general, epilepsy can be controlled with anti-convulsant drugs that lessen the frequency of seizures. Sometimes a combination of drugs is necessary. Complete control of seizures can be achieved in up to 50 percent of patients; another 25 percent can be improved significantly; the remainder are incompletely controlled and suffer considerable disability. Surgery is considered in the roughly 10 percent of patients who do not respond to drugs.

Major Depression

This affliction, with its harrowing feelings of sadness, hopelessness, pessimism, loss of interest in life and reduced emotional well-being, is one of the most debilitating mental disorders. It is as disabling as coronary disease or arthritis. Depressed individuals are 24 times more likely to attempt suicide than people with no mental illness.

In any one-month period, major depression affects nearly 3.5 million American adults and young people. Fortunately, 80 percent of patients respond to drugs, psychotherapy or a combination of the two. Some severely depressed patients can be helped with electroconvulsive therapy.

Depression arises from many causes: biological (including genetic), psychological, environmental or a combination of these. Stroke, hormonal disorders, birth control pills and sleeping pills can also play a part.

Physical symptoms — disturbances of sleep, sex drive, appetite and digestion — are common. Some of these symptoms may reflect the fact that the disorder affects a delicate hormonal feedback system linking the hypothalamus, the pituitary gland and the adrenal glands.

The modern era of drug treatment for depression began in the late 1930s. A new generation of drugs now allows individualized treatment and a much greater chance of success for the more than 8 million Americans who suffer from major depression or other mood disorders.

Most antidepressants affect norepinephrine and serotonin in the brain, apparently by correcting the abnormal excess or inhibition of the signals that control mood, thoughts, pain and other sensations. *Imipramine*, a *tricyclic* antidepressant, primarily blocks the reabsorption of norepinephrine and may affect serotonin levels.

Another class of antidepressant medications is the *monoamine oxidase inhibitors* (MAOIs). During the 1950s, the first of the MAOIs, *iproniazid*, was found to make experimental animals hyperalert and hyperactive. By 1957, scientists had proven iproniazid's benefit in patients. Today, three MAOIs are available for use.

MAOIs are thought to be more complicated than tricyclics. These agents inhibit *monoamine oxidase*, a substance that breaks down serotonin, norepinephrine and dopamine, allowing these chemicals to remain active.

A recently developed medication, *fluoxetine*, is the first of a new class of drugs, *serotonin reuptake inhibitors*. Fluoxetine is believed to zero in on serotonin and keep it active in certain brain circuits. For many patients, this drug seems to restore overall serotonin activity to a more normal state and alleviate depression.

Patients with manic depression usually alternate between episodes of deep depression and periods of mental and physical hyperactivity, with a return to relatively normal functioning in between. Since 1970, manic-depressives have greatly benefited from the use of *lithium*.

CHALLENGES

ADDICTION. Universally regarded as the nation's most serious health problem, the abuse of alcohol and drugs by millions of Americans was estimated for 1988 to cost more than $144 billion, including the costs of treatment, prevention, lost productivity and violence.

Drug addiction is one of the most difficult conditions to understand. For decades, researchers have unsuccessfully sought to uncover an addictive personality to forecast early warnings of risk. Personality traits, genetic susceptibility and how drugs enter the chemical pathways of the brain's pleasure centers remain topics of intense research.

While causes remain elusive, scientists do know the signs of addiction: physical dependence and psychological dependence. Physical dependence is an adaptive state that shows itself by intense withdrawal symptoms when the administration of the drug is stopped. Psychological dependence is a craving for a drug in order to produce pleasure or to avoid discomfort. A third aspect of drug dependence is tolerance, the requirement with chronic use for progressively higher drug doses to achieve a given effect.

Alcohol • Roughly 15 million Americans have an alcohol problem — 6 million abusers and 9 million who are alcohol-dependent — and some 100,000 people die from it each year. *Fetal alcohol syndrome*, which causes mental retardation and facial deformities, affects about one in every 500 babies born in the United States. Chronic liver disease and cirrhosis, the main chronic health hazards associated with alcohol abuse, were the nation's ninth leading cause of mortality in 1988, responsible for more than 26,000 deaths. The cost of alcohol dependence and abuse in 1988 was estimated at $85.5 billion.

Both genetic and environmental factors contribute to alcoholism but no single factor or combination of factors has allowed doctors to predict who will become an alcoholic.

Ethanol, alcohol's active ingredient, is a depressant that acts to reduce anxiety, tension and inhibitions — significantly altering mood and behavior. Its other effects include stimulation of appetite, heat loss and dehydration.

Alcohol is easily absorbed into the bloodstream and the brain, yet a precise mechanism for this is unclear. It was once widely believed that alcohol acted on all neural membranes, perhaps altering their electrical excitability. Now, many scientists believe that alcohol's interaction with the GABA receptor enhances this neurotransmitter's inhibitory action. In addition, dopamine, the NMDA receptor and glutamate are believed to be involved.

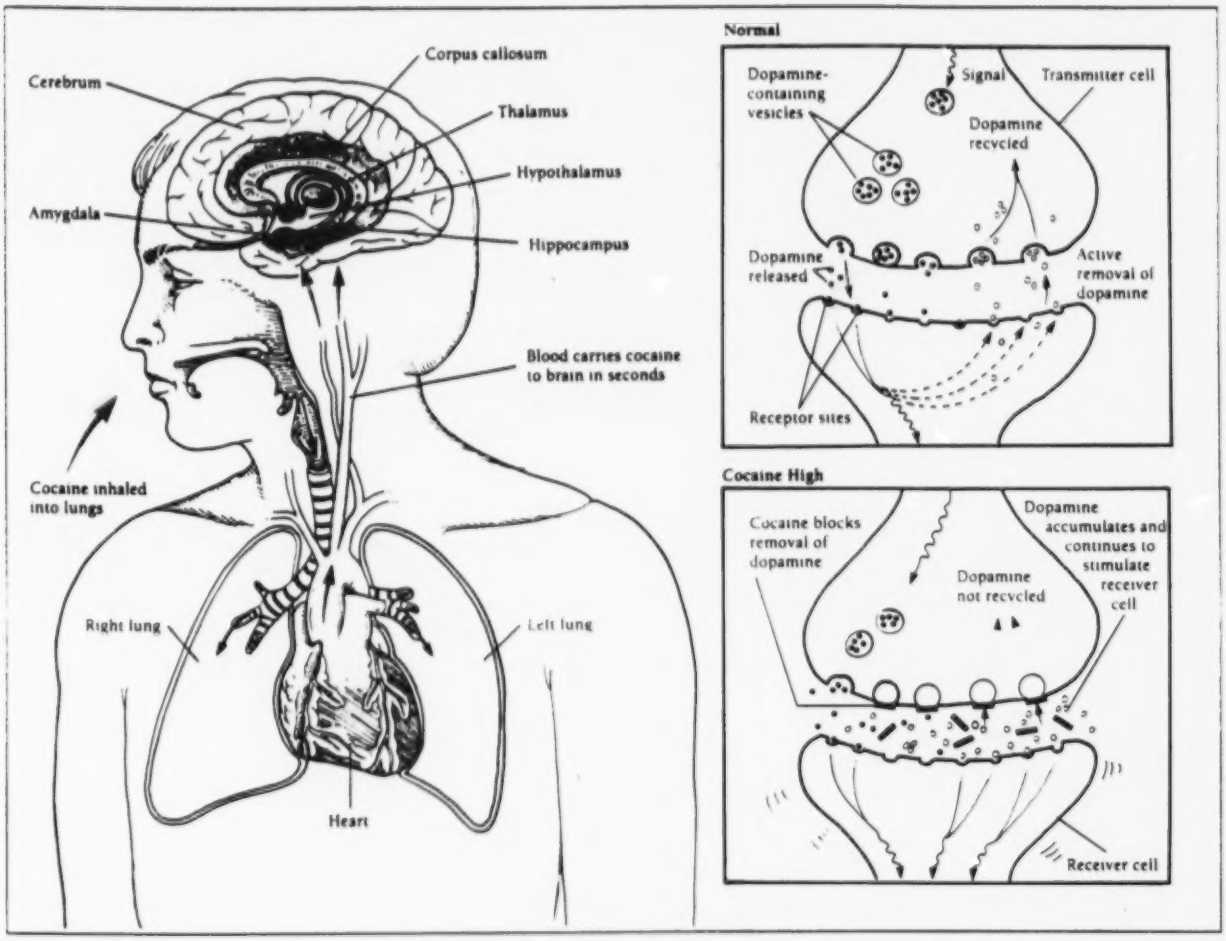
While several drugs are used to treat alcoholism, they are unlikely to be effective in producing a long-term reduction in drinking behavior. Current treatment strategies manage withdrawal; foster sobriety; decrease drinking by treating psychiatric problems; and attenuate problem drinking behavior itself. All are considered adjuncts to other treatments.

Counseling, psychotherapy and Alcoholics Anonymous are the traditional approaches that form the standard treatment. The first step is for the individual to recognize he or she has a problem in need of help. Then a broad-based approach includes changing drinking behavior and the individual's environment in ways to maintain sobriety. Because alcoholics often receive a variety of treatments, it is difficult to compare the absolute effectiveness of one therapy with another.

Psychostimulants • While researchers note a drop-off of cocaine use in the United States — from 5.8 million users in 1985 to 2.9 million in 1988 — use of the drug has become more intense.

Part of the reason users crave psychostimulants (cocaine and amphetamines) is to counter symptoms similar to a major depression — decreases in activity and initiative, excessive drowsiness, increased appetite, feelings of unhappiness and inability to experience pleasure — that occur when a binge ends.

One biochemical factor that seems to reinforce the effects of psychostimulants is dopamine. Neurons containing dopamine that project into the limbic system and frontal cortex are required for the acute reinforcing actions of cocaine and amphetamines. Scientists suggest that some abnormalities within the dopamine system can sensitize individuals to the reinforcing actions of these drugs. Many scientists believe the ability of cocaine to block reabsorption of dopamine overexcites nearby neurons to produce euphoria. The crash



How Crack Cocaine Affects The Brain. Cocaine enters the bloodstream through the lungs. Within seconds it is carried to the brain where it acts in the limbic system, the brain's "pleasure pathway." The effect occurs at synapses where impulses are passed from one neuron to another. Normally, (above, right) a transmitting cell in the limbic system relays a signal by releasing dopamine into the synaptic space. Dopamine crosses the space and fits into receptors on the surface of the receiving cell. This triggers an electrical signal that is relayed through the receiver. Then, to end the signal, dopamine molecules break away from the receptors and are pumped back into the nerve terminal to be recycled. Cocaine molecules (below, right) block the pump or "transporter" by which dopamine again enters the nerve terminal. They bind to the dopamine transporter, causing more dopamine to accumulate in the synaptic space. This continually stimulates the receiving cell, ultimately causing a "high."

occurs when the dose needed to restore the high becomes greater than the user can find, or from exhaustion. The neurochemical basis of the crash is still unclear.

Dopamine receptors — located in the brain's ventral tegmental area, nucleus accumbens, amygdala, hypothalamus and pituitary — are implicated in this activity. Amphetamine produces a similar effect but can also release dopamine and norepinephrine.

Scientists are anxiously trying to find drugs that block the effects of cocaine or lessen the ensuing depression. Some drugs block the effects of cocaine in animals but most cocaine-dependent people do not want to take them because they produce serious side effects. Moreover, the patient will remember how good he or she felt when still a user.

The most effective treatment programs, experts say, are those that employ three separate stages: detoxification; extended personal counseling combined with vocational guidance and training; and community support groups. New antidepressants usually help during the first weeks of therapy. Still, some of the best programs have drop-out rates of 50 percent or more and the number of addicts who return to drug use is very high.

Opiates • These drugs, derived from the opium poppy, have been used by humans for centuries. Monkeys and rats readily self-administer them and will become physically dependent with unlimited access. Unlike psy-

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chostimulants, humans and animals allowed only limited access will maintain a stable level and pattern of intake. When interrupted, this causes neither tolerance nor physical dependence. In contrast, unlimited access produces profound tolerance, leading to increased intake and severe withdrawal symptoms. When stopped, withdrawal symptoms range from mild flu-like discomfort to major physical signs, including severe muscle pain, stomach cramps and diarrhea. Regions of the brain active in the reinforcing actions of psychostimulants play the same role with opioids.

Doctors know that drugs such as *nalorphine*, *naloxone* and *cyclazocine* block the effects of morphine, heroin and other narcotics. The problem is that an addict must be highly motivated to take the opioid-blocking drug.

Standard treatment involves methadone maintenance which in theory helps rehabilitate addicts by preventing withdrawal symptoms and by blocking the pleasurable effects of opiates. The treatment is controversial, however, because many believe it condones continuing dependence on narcotics and creates an even greater level of tolerance.

Stroke

If your grandfather had a stroke today, his doctor would tell the family there was no treatment. In all likelihood, the patient would live out his remaining months or years with neurological impairment.

While researchers have not yet found a magic bullet for stroke, attitudes toward the nation's third leading cause of death are changing rapidly. Preventive measures have reduced the frequency of stroke. New experimental drug therapies show promise for improving recovery afterward.

Stroke affects roughly 500,000 Americans a year, 150,000 of whom die; total costs per year are estimated at $25 billion.

It often occurs in individuals over 65 years of age, yet a third are under age 65 and in their most productive years. Stroke tends to occur more in males, blacks, and those with diabetes, high blood pressure, heart disease, obesity, high cholesterol and a family history of stroke. Controlling risk factors such as obesity, blood pressure, diabetes and high cholesterol can help prevent this disorder.

Treatment involves several techniques. If atherosclerotic plaque has caused blockage in the arteries of the neck region, surgery might be used to clear them to prevent the likelihood of a clot causing a cut-off of blood supply. Blood-thinning drugs, such as *heparin*, may be the choice when a blood vessel has been blocked or blood clots are a problem. These drugs help prevent new clots from forming or an existing clot from enlarging.

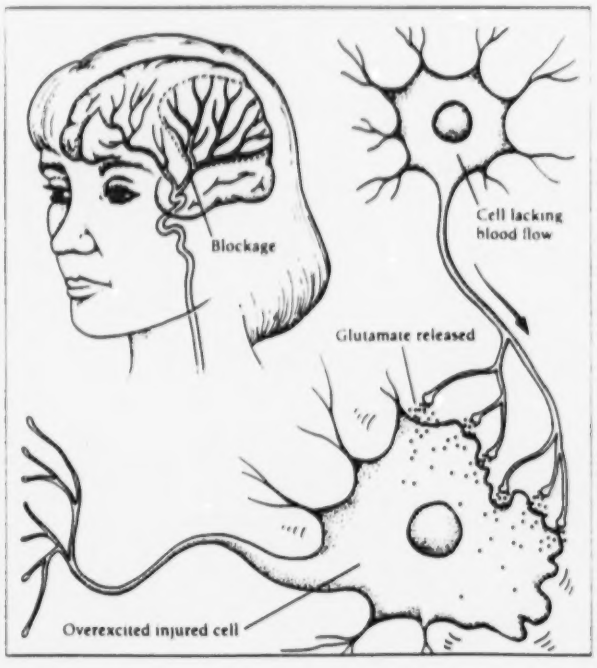
Sometimes treatment means therapy for the heart because heart disease contributes to stroke. Damaged valves may need surgery or drugs to reduce the chance of clots forming around the valves that then travel to the brain and cause a stroke.

A recent study found that daily doses of *aspirin* or another blood-thinning drug called *warfarin* could prevent thousands of strokes every year in people suffering from *atrial fibrillation*. Patients with this condition, in which the heart beats irregularly and ineffectually, are at higher risk of stroke because stagnant pools of blood collect in the heart and increase the likelihood of clot formation. In the study, aspirin cut the risk of stroke by 80 percent.

While doctors can do little to restore permanently damaged brain neurons, a good rehabilitation program can make the difference between institutionalization and returning home. Yet stroke remains a considerable challenge, with an initial 30-day mortality averaging 38 percent. Of patients who survive this critical period, long-term survival is 50 percent. And as the age of the population increases, these rates are rising.

New drugs now under study could lead to a dramatic

STROKE. A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot or some other particle. This lack of blood causes cell death within minutes. The cells closest to the injury die of oxygen deprivation. One theory of cell death is that the overexcited dying cells release neurotransmitters, especially glutamate, to nearby cells. These nearby cells become overexcited, swollen and die, and this is one of the places where scientists think they can stop the process of cell death. Depending on its location, a stroke can cause many disorders; for example, paralysis on one side of the body and loss of speech. The effects of stroke are often permanent because dead brain cells are not replaced.



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shift in these statistics by staving off the irreversible brain damage that occurs in patients with stroke or head injuries.

One approach involves rapidly opening blocked vessels to restore circulation before oxygen loss causes permanent damage. Use of clot-dissolving agents — the bioengineered drug *tissue plasminogen activator* (TPA), or *streptokinase*, an enzyme derived from streptococcal bacteria — may soon become standard treatments in many hospitals. TPA given within 90 minutes of a stroke has already shown promising results in pilot studies.

Another strategy is to slow cell death by interrupting the chain reaction initiated by a dying cell: the release of abnormally high amounts of glutamate that can kill neighboring brain cells by overstimulating glutamate receptors.

Several agents are being tested for their ability to block the NMDA receptor where glutamate is recognized. Still others are aimed at targets within the cell. In this way, the vicious cycle of local damage followed by a widening fringe of glutamate-induced neuronal death can be slowed. Thus far, most of these compounds have been tested only in animals. It will be years before their value is known to humans.

Neurological Trauma

As with stroke, no magic bullet has been found, but doctors have discovered several methods to stave off severe neurological damage caused by head and spinal cord injuries. These treatments include better emergency care, improved rehabilitation and a drug that was recently found to help reduce damage in spinal cord injuries.

Some 500,000 people receive traumatic head injures requiring hospitalization each year; and roughly 100,000 die — many before reaching the hospital. Economic costs approach $25 billion annually.

Greater use of newer imaging methods enables doctors to more readily see swelling that is potentially life-threatening and act immediately. They can bore a small hole in the skull and insert a tube hooked up to a pressure monitor. When the intracranial pressure is above safe levels, the patient is put on a ventilator to increase the breathing rate. The more breaths a patient takes, the more carbon dioxide is blown off, helping to shrink cerebral blood vessels and thus reduce intracranial pressure. Drugs such as *mannitol* help draw water away from the brain.

Spinal cord injuries affect some 10,000 Americans annually, mostly males under age 30 who are hurt in automobile accidents, at a total cost of $2 billion.

Researchers recently reported that people who suffer spinal cord injuries become less severely paralyzed if they receive high intravenous doses of a steroid drug within eight hours after injury. The drug *methylprednisolone* appears to help regardless of how severely the spinal cord is injured and, in some cases, makes the difference between a patient being confined to a wheelchair and being able to walk.

Building on this knowledge, researchers hope to decipher the precise order of the chemical reactions that lead to injury. Once they understand the factors that prohibit regrowth of spinal fibers, they hope to develop drugs that block these reactions and allow regeneration.

Alzheimer's Disease

One of the most frightening and devastating of all neurological disorders, dementia caused by Alzheimer's affects an estimated 4 million Americans. The cause and effective treatments are still under investigation for this mysterious disorder which takes 100,000 lives a year and is one of the nation's leading killers of adults. It is expected to affect 14 million Americans by the year 2040.

Forgetfulness and memory loss, time or place disorientation and difficulty with concentrating or calculating are the earliest symptoms which usually begin during the patient's mid-60s. Final stages leave the victim incapable of self-care. Death usually results from pneumonia or some other complication.

TO DEVISE BETTER TREATMENTS FOR STROKE, SCIENTISTS STUDY THE CHEMICAL REACTIONS THAT LEAD TO NERVE CELL DEATH.

Preliminary diagnosis can be made while the patient is still alive but absolute confirmation of Alzheimer's requires an autopsy of the brain. Examination shows abnormal protein accumulation, *neurofibrillary tangles* in neurons and clusters of degenerating nerve endings, *neuritic plaques*, in the areas of the brain important for memory and intellectual function. Abnormal deposits of *amyloid protein* are linked to the plaques and are either responsible for them or related to the cause of the disorder.

Alzheimer's brains have lower than normal levels of acetylcholine, somatostatin and monoamines — due to loss of the specific cell groups that synthesize these transmitters in the brainstem.

The cause of neuron death is unknown. Possibilities include cell membrane defects, protein processing problems, heredity, immune system problems and neurotoxic substances. At most, 10 percent of victims have an inherited form which starts earlier in life and progresses rapidly. A genetic marker for one type of this hereditary form has been located on chromosome 21.

A preliminary diagnosis can be made in 90 percent of cases through a medical history, physical and neurological exams and a mental status test. *Computerized tomography* (CT) and *magnetic resonance imaging* (MRI) scans show reduced cerebral size.

Presently, there is no treatment for the cognitive symptoms but research on drugs called *cognitive enhancers* is proceeding rapidly based on detailed studies in aged animals of anatomical and biochemical circuits involved in cognitive processing and memory.

For now, agitation, anxiety and unpredictable behavior, sleep disturbances and depression that accompany the disease can be treated.

At least a dozen drugs offering palliative treatment are under study. Two that are furthest along in development are *tetrahydroaminoacridine* and *physostigmine*, which help restore acetylcholine. Animal tests with *nerve growth factor* (NGF), a naturally-occurring protein necessary for the growth and maintenance of certain neurons, are underway. NGF has nourishing effects on brain neurons that release acetylcholine. Unfortunately, the only way to get the drug into the brain is by direct injection, a procedure not usually recommended for humans. In another approach, researchers are considering transplanting tissue which could release missing neurotransmitters or growth factors directly into the brain. In theory, this technique could restore neurotransmitter function and prevent brain cells from dying.

Early diagnosis of Alzheimer's through use of biochemical tests or CT and MRI scanning may soon permit doctors to combat the disease when drugs become available. Scientists recently reported the discovery of an early "marker", a decrease in the size of the hippocampus in deceased Alzheimer's patients compared with patients who died without suffering this disorder. Other tests detect abnormal proteins unique to Alzheimer's.

Since aged monkeys have plaques and tangles, several centers conduct research on them to assess age-related memory decline and drugs that ameliorate this condition.

Anxiety and Panic Disorders

The most widespread mental illnesses, anxiety disorders affect an estimated 7.3 percent of the U.S. adult population, 11.5 million Americans, in a one-month period. They include *phobias*, *panic disorder* and *agoraphobia* and *obsessive-compulsive disorder*. Some can keep people completely housebound or, as in the case of panic disorder, contribute to suicide.

In obsessive-compulsive disorder, people become trapped in repetitive thoughts and behaviors they recognize as groundless but cannot stop, such as washing hands or checking doors or stoves. The illness is thought to affect more than 2 million Americans in any one-month period. Social learning and genetics may play a role in developing the disorder. But PET scans reveal abnormalities in both cortical and deep areas of the brain, suggesting a biological component as well.

Panic disorder — which affects nearly 800,000 Americans during a one-month period — usually starts "out of the blue." Patients experience an overwhelming sense of impending doom, accompanied by sweating, weakness, dizziness and shortness of breath. With repeated attacks, patients may develop anxiety in anticipation of another attack and avoid public settings where attacks might occur. Untreated, their lives may constrict until they fear leaving home for any reason.

The recent discovery of brain receptors for the benzodiazepine antianxiety drugs has sparked research to identify the brain's own antianxiety chemical messengers. This finding may lead to ways to regulate this brain system and correct its possible defects in panic disorder. PET scans reveal that during such attacks, the tip of the brain's temporal lobe is unusually active compared with controls. When normal people expect to receive a shock to the finger, the same general area is activated.

For both obsessive-compulsive disorder and panic disorder, behavioral and drug treatments show promise separately and in combination but their effectiveness is still under investigation.

Schizophrenia

Marked by disturbances in thinking, emotional reactions and social behavior, schizophrenia almost always results in chronic illness and personality change. Delusions and hallucinations are common.

Affecting less than one percent of the population or 1.1 million Americans in a one-month period, schizophrenia is disabling and costly. On a given day, these patients occupy more than 100,000 hospital beds. Annual treatment costs exceed $7 billion, while lost productivity and other losses exceed $14 billion.

Schizophrenia is thought to reflect changes in the brain caused by disease or injury at the time of birth or a genetic disposition exacerbated by environmental stress. Brain systems using dopamine appear to be particularly involved. Scans and postmortem studies show abnormalities in schizophrenics, such as enlarged cerebral ventricles (fluid-filled spaces) and reduced brain size. PET scans show that the prefrontal cortex of schizophrenic patients is not properly activated in response to intellectual tasks.

The disorder usually begins between ages 15 and 25. Some patients fully recover following treatment but most continue to have moderate or severe symptoms, particularly in response to stress.

After a long search for a strong antipsychotic agent, scientists synthesized the drug *chlorpromazine* during the late 1940s. By the 1950s, it was found useful for treating psychotic states and later became a mainstay of drug treatment.

Since then a large number of agents similar to chlorpromazine have been developed. When given as long-acting injections, these drugs reduce some symptoms and aid patients' readiness for adjustment back in the community. However, chronic use may cause abnormal muscle movements and tremors in some patients. Safer treatments are being sought.

Thus far, most drugs are successful in calming "positive" symptoms such as hallucinations and agitation. A new drug, *clozapine*, acts differently from other antipsychotics. It is the first medication to alleviate "negative" symptoms: lack of motivation, loss of emotion and social withdrawal. And clozapine appears to help the 10 to 20 percent of patients who are not helped by conventional medications. However, the drug can induce a potentially fatal blood disorder, *agranulocytosis*, in about 1 percent of patients. To prevent this, patients must take regular tests of blood and bone marrow function, a precaution that makes the use of the drug very costly.

Neurological AIDS

By the end of 1993, as many as 480,000 AIDS cases and 340,000 deaths from AIDS will have occurred in the United States. Unfortunately, the nervous system as well as the immune system is profoundly affected by this virus. Medical experts estimate that 20 to 66 percent of patients with full-blown AIDS also develop dementia which often includes movement impairment. Nearly all patients with this syndrome have mental problems ranging from mild to progressive, fatal, dementia.

And in spite of advances made in treating other aspects of the disease, AIDS dementia remains a mystery. Physicians still do not know why it happens and until they do, they won't be able to adequately prevent or treat it.

Experts believe that serious neurologic symptoms are uncommon early in AIDS infection. But later, patients develop leg weakness, loss of balance, difficulty concentrating, apathy, irritability and depression-like symptoms. CT and MRI scans and the examination of brain cells under a microscope suggest that the dementia occurs principally in sub-cortical areas, with marked changes in the myelin.

The anti-AIDS drug AZT has reversed some nervous system symptoms but the effect is short-lived. Preliminary clinical trials are now underway testing AZT and several other compounds.

Multiple Sclerosis

The most common central nervous system disease of young adults after epilepsy, this life-long ailment of unknown origin affects one in 1,000 adults, thus disabling more than 250,000 Americans. Multiple sclerosis (MS) strikes mainly between the ages of 20 and 40, with two of three cases occurring in women. It results in earning losses for families with MS of about $2 billion annually.

While a cause has yet to be found, MS is thought to be an autoimmune disease in which the body's natural defenses act against the myelin in the central nervous system as though it were foreign tissue. The myelin, which surrounds and insulates nerve fibers of the brain and spinal cord, begins to disintegrate and interfere with nerve signals by distorting or blocking them.

Genetic and environmental factors have also been suggested. Siblings of affected people are 10 to 15 times more likely than others to come down with MS. The disease is five times more prevalent in temperate zones (such as the U.S. and Europe) than in the tropics. A viral infection acquired during the first 15 years of life may be responsible for triggering the disease which becomes apparent later.

The most common symptoms are blurred vision, awkward gait, numbness and fatigue. These can occur singly or in combination, vary in intensity and last from several weeks to months. In some patients, symptoms include slurred speech, weakness, loss of coordination, uncontrollable tremors, loss of bladder control, memory problems, depression and paralysis. Muscle spasticity can affect balance and coordination, causing pain, involuntary jerking movements and severe *contractures*, freezing of a joint that prevents movement.

MS is incurable but there is help for some symptoms until definitive treatment is available. Muscle relaxants and tranquilizers alleviate muscle spasticity; *adrenocorticotropic hormone* (ACTH) and steroids help shorten attacks by reducing inflammation; and stretching exercises and physical therapy help keep muscles in working order. Other agents help kill pain.

Several compounds which suppress the immune system are being tested in patients. One of the promising treatments is a synthetic version of the protein myelin that desensitizes the malfunctioning immune system. In early studies, doctors found it lessens flare-ups in some patients; they hope it may prove broadly useful. Other drugs under study include interferons and a combination of the drug *cyclophosphamide* and ACTH.

Down Syndrome

This form of mental retardation caused by a genetic defect occurs about once in every 800 live births and affects some 250,000 American families.

The most common form of Down's, *Trisomy 21*, results when the egg or sperm adds an extra chromosome, producing mental impairment and these physical signs: a drawing of the arms across the chest in an embracing manner, low nasal bridge and small nose, eyes that slant upwards, deep creases across the center of the palm and excessive ability for flexing extremities.

The risk of having a child with Down's increases with the age of the mother. At age 35 the risk is one in 400

births; at age 40, it is one in 110. Highly accurate prenatal tests, chorion villus sampling performed between the eighth and twelfth weeks of pregnancy or amniocentesis between the thirteenth and fifteenth weeks, can determine if a fetus is likely to be affected.

Medical advances have produced effective treatments for the improper heart development, susceptibility to infection, respiratory problems and immature digestive tracts, which may affect people with Down's.

The degree of mental retardation varies widely, with the majority falling in the moderate range. Children with Down's learn to sit, walk, talk and toilet train, although usually at a later stage than average.

Early intervention from birth, quality education programs, a stimulating home environment and good medical care has boosted survival from nine years in 1910 to an average of 55 years today. Many people with Down's are active and productive.

Although there is no cure, scientists are moving closer to identifying the genes on chromosome 21 responsible for the syndrome. Once identified, they hope to decode the biochemical processes responsible and eventually treat or cure the disorder.

Huntington's Disease

Afflicting some 25,000 Americans, with another 125,000 at risk, Huntington's is one of the more common inherited brain disorders. This slowly progressing disease, which causes the degeneration of brain cells, usually starts between ages 30 and 50. It affects neurons in the basal ganglia, an area important for movement coordination, and in the cortex, the center for thought, perception and memory.

The most recognizable symptoms are involuntary jerking movements of the arms, legs, torso and facial muscles. These are often accompanied by mood swings, depression, irritability, slurred speech and clumsiness. Later on, common symptoms include swallowing difficulty, unsteady gait, loss of balance, impaired reasoning and memory problems. Eventually, the victim is confined to a bed or wheelchair, with death often due to pneumonia, heart failure or some other complication.

Diagnosis entails a clinical examination and detailed family history. CT and PET scans may help. Discovery of a genetic marker for Huntington's on chromosome 4 allows for a predictive test using blood or tissue from the person at risk and relatives. Predictive testing is available for adults at risk; prenatal testing can also be performed. The test may be accurate up to 99 percent but raises some ethical issues — especially about the value of a predictive test for a disease that currently has no cure.

Until the mutant gene is identified, treatment focuses on helping people with Huntington's live longer at a better level. This includes physical and occupational therapy, learning how to swallow appropriately, balance exercises, maintaining proper weight and various medications for depression, hallucinations and stress.

In addition to hunting for the gene, researchers are pursuing various treatments. In one set of experiments, scientists are focusing on *quinolinic acid*, a brain neurotoxin that excites NMDA receptors and is not harmful under normal conditions. Since very high levels of quinolinic acid are found in the brains of Huntington's patients, researchers believe excitation may be excessive or prolonged. They are actively searching for ways to block this toxic effect.

HUNTINGTON'S DISEASE, ONE OF THE MORE COMMON INHERITED BRAIN DISORDERS, HAS BEEN TRACED TO GENETIC MARKERS ON CHROMOSOME 4.

Tourette Syndrome

One of the most common and least understood neurological disorders, Tourette's is a genetic condition that affects an estimated 100,000 Americans, including some 20,000 youngsters. Males are affected three to four times as frequently as females.

The disorder usually appears between ages four and eight, but may emerge as late as age 21. Symptoms include motor and vocal tics that are repetitive, involuntary, rapid and sudden movements or utterances. A majority of patients have a mild form of the disorder with symptoms of excessive eye blinking, shoulder twitches or shrugging or noise-making. Many of these tics can be controlled in the same way that a sneeze can be held in. More extreme forms of Tourette's, which are relatively rare, can seriously interfere with everyday living. Additional symptoms include self-injury and uttering obscenities.

Since the defective gene is not yet identified and no laboratory test can identify the syndrome, diagnosis is made by observation. Some tests can rule out other possibilities.

Haloperidol, a neuroleptic drug, has been the mainstay of treatment. It is not an ideal drug, however, because it produces disturbing side effects — abnormal involuntary movements, stiffness of the face and limbs, or sedation in some patients. The disorder seems to result from hypersensitivity of dopamine receptors. Most effective drugs, such as haloperidol, act by blocking the overactive system. Other symptoms, such as obsessive-compulsive traits and attention deficit disorder, often need treatment with other classes of drugs.

New Diagnostic Methods

Many of the recent advances in understanding the brain are due to the development of anatomical techniques that allow scientists to see more clearly the many connections between neurons throughout the body.

Electrophysical recordings trace brain electrical activity in response to a specific external stimulus. In this method, electrodes attached to specific parts of the scalp — depending on which sensory system is being tested — make recordings that are then processed by a computer. The computer makes an analysis based on the time lapse between stimulus and response. It then extracts this information from background activity.

Following the discovery that material is transported within neurons, methods have been developed to visualize activity and precisely track fiber connections within the nervous system. This can be done by injecting a radioactive amino acid into the brain of an experimental animal; the animal is killed a few hours later; and then the presence of radioactive cells is visualized on film. In another technique, the enzyme horseradish peroxidase is injected and taken up by nerve fibers which can be later identified under the microscope.

While the use of these and other methods has resulted in many advances in knowledge about the workings of the nervous system and are still useful today, new methods promise to give even more precise information about the nervous system, particularly the point of origin of disorders such as epilepsy.

Imaging Techniques

Positron Emission Tomography • This method of measuring brain function is based on the detection of positively charged particles emitted by radioactively labeled substances introduced into the body. PET scanning produces a three-dimensional image that reflects metabolic and chemical activity in the brain.

In this technique, doctors inject into the bloodstream trace amounts of natural body compounds or specific drugs labeled with a radioactive isotope. Since these isotopes have a relatively short half-life (two to 110 minutes), an accelerator must be nearby to produce them so the studies can be conducted rapidly.

These labeled compounds are taken up in brain tissue in greater concentrations by areas that are more metabolically active. In tissue, these substances emit positively charged particles called positrons. In turn, positrons emit photons that are detected by the scanning machine.

One PET technique measures the metabolism of glucose, the brain's fuel, and converts this information by computer to a three-dimensional, color-coded picture of brain activity. The brightest colors indicate the brain areas most active while subjects are performing specific tasks.

So far, PET studies have helped scientists understand more about how drugs affect the brain and what happens during learning, language and certain brain disorders.

For instance, when compared to normal patients, people who experience panic attacks have greater blood flow and metabolism in a very specific area of the right side of the brain than in the left, even when they are not having an attack. During an acute episode of anxiety, both normal subjects with anxiety and patients with panic attacks seem to engage a similar portion of the cortex, the temporal lobe.

PET should soon enable scientists to identify the biochemical nature of neurological and mental disorders and determine how well therapy is working in patients.

Another technique, *single photon emission computer tomography* (SPECT), is similar to PET but its pictures are not as detailed. SPECT is much less expensive than PET because the tracers it uses have a much longer half-life and do not require expensive machinery to produce them.

Magnetic Resonance Imaging • Providing a high quality three-dimensional image of organs and structures inside the body without X-rays or other radiation, MRI images are unsurpassed in anatomical detail and may reveal minute changes that occur with time. MRI is expected to tell scientists when structural abnormalities first appear in the course of a disease, how they affect subsequent development and precisely how their progression correlates with mental and emotional aspects of a disorder.

During the hour-long MRI procedure, a patient lies inside a massive, hollow, cylindrical magnet and is ex-

posed to short bursts of a powerful magnetic field. The protons of the body's hydrogen atoms normally point randomly in different directions, but in a magnetic field they line up parallel to each other like rows of tiny magnets. If the hydrogen nuclei are then knocked out of alignment by a strong pulse of radio waves, they produce a detectable radio signal as they fall back into alignment.

Magnetic coils in the machine detect these signals and a computer changes them into an image based on different types of body tissue. Tissue containing high levels of hydrogen (such as fat) produces a bright image; that containing little or no hydrogen (such as bone) appears black. (The image is similar to that produced by CT scanning but MRI generally gives greater contrast between normal and abnormal tissues.) MRI allows images to be constructed in any plane and is particularly valuable in studying the brain and spinal cord. It reveals tumors rapidly and vividly, indicating their precise extent. MRI also produces impressive images of the eye and ear.

Magnetic resonance spectroscopy (MRS), a technique related to MRI which uses the same machinery but examines chemistry rather than anatomy, also holds great promise to provide insights into how the brain works. By measuring the chemical and energy changes that occur in the brain, MRS has already provided new information on brain development and aging, Alzheimer's disease, schizophrenia, autism and stroke. Because it is safe and non-invasive, this method is ideally suited to study the natural course of a disease or its response to therapy.

Magnetic Source Imaging • One of the latest advances in scanners, magnetic source imaging (MSI) reveals the source of weak magnetic fields emitted by neurons firing electrical signals. An array of cylinder-shaped sensors monitors the magnetic field pattern near the patient's head to determine the positions and strengths of activity in various regions of the brain. By tracking the magnetic fields, scientists can determine the origin of epileptic seizures and responses to sound, touch and vision.

MSI could benefit as many as 200,000 epileptics whose seizures often can be prevented by surgery that removes the area of the brain causing the disorder. It is also useful in characterizing certain hearing disorders such as tinnitus, a constant ringing sound in the ears.

Gene Diagnosis

The inherited blueprint for all human characteristics, genes consist of short sections of *deoxyribonucleic acid* (DNA), the long, spiraling, chainlike structure found on the 23 pairs of *chromosomes* in the nucleus of every human cell. All of an individual's genes come from his or her parents and hold the information for every aspect of bodily growth, development, function, reproduction and possibly for aging and death. Genes achieve their effect by directing the manufacture of proteins. Differences in gene structure are responsible for the physical differences between people such as eye, hair and skin color. So too, changes in gene structure, known as mutations, are responsible for many neurological and psychiatric disorders.

New gene diagnosis techniques now make it possible to find the chromosomal location of genes responsible for neurologic and psychiatric diseases and to identify structural changes in these genes.

This information is useful for detecting individuals who carry the mutant gene, prenatal diagnosis, classifying disease and evaluating certain tumor types and their stage. Moreover, these methods bode well for eventually defining the molecular mechanisms involved in the disease process.

Significant progress has been made in identifying the regions on chromosomes carrying the defects that result in roughly two dozen neurological disorders but prenatal or carrier tests exist for only a handful.

In Huntington's disease, scientists have tracked down markers on chromosome 4 that are very close to the mutant gene ("linked") in affected members of three generations in a number of different families. At this time, however, for a person at risk to be tested, sufficient numbers of family members must be alive to carry out the tests. Although the linkage tests can not predict risk with 100 percent certainty, carrier and prenatal testing has begun at medical centers in the United States, Canada and Europe.

Sometimes patients with single gene disorders are found to have a chromosomal abnormality — a deletion or break in the DNA sequence of the gene — that can lead to a change in genetic material that disrupts its normal activity.

Such is the case of some abnormalities found on the X-chromosome in patients with Duchenne muscular dystrophy and on chromosome 13 in patients with *inherited retinoblastoma*, a rare childhood eye tumor that leads to blindness. A chromosomal abnormality also has been located for *myotonic dystrophy*, symptoms of which include spasms, muscle wasting and cataracts.

Gene mapping has led to the localization on chromosome 21 of the gene encoding the precursor to amyloid, the peptide that accumulates in senile plaques in Alzheimer's disease. This discovery shed light on the reason why individuals with Down syndrome (Trisomy 21) invariably accumulate amyloid deposits; they make too much amyloid as a consequence of having three copies instead of two copies of the gene. Although no mutation of the amyloid gene has been associated with Alzheimer's, this gene is the site of the mutation in a rare, allied disorder — *hereditary cerebral amyloidosis with stroke*.

Overall, the characterization of the structure and function of individual genes causing neurological disorders is in the early stage. And factors that determine variations in the genetic expression of a single-gene abnormality — such as what contributes to the early or late start or severity of a disorder — are unknown.

Potential Therapies

New Drugs. Most drugs in use today have been screened using time-consuming techniques in experimental animals which do not always reveal precisely why a drug produces a particular effect. But the expanding knowledge of neurotransmitter receptors and new methods of molecular biology — the ability to clone a receptor gene and determine its molecular structure — make it possible in principle to design much better agents.

In a test tube, the potency of an agent can be determined by how well it binds to a receptor site. A pharmacologist then can vary the drug's molecular structure to enhance its effect on that particular receptor. Thus, subsequent generations of test drugs can be designed to interact with receptors more efficiently and are likely to exhibit higher potency with fewer side effects.

While this so-called "rational drug design" holds promise for developing drugs for conditions ranging from migraine headaches and depression to fear and anxiety, it will take considerable time and effort to clarify the role of different receptors in these disorders.

Neurotrophic Factors

These body chemicals, which stimulate the growth and survival of specific neurons, are one of the most exciting areas of brain research. They hold promise for treating a wide array of neurodegenerative diseases. Scientists have identified half a dozen substances that appear to be neurotrophic factors and expect to find many more.

Already, researchers have demonstrated the possible value of at least one of these factors, *nerve growth factor* (NGF). Infused into the brains of rats, NGF has prevented cell death and stimulated the regeneration and sprouting of damaged neurons that release acetylcholine. When animals with learning and memory impairments from brain lesions were treated with NGF, scientists found that the rats were able to remember a maze task as well as healthy rats. A human recombinant NGF has the same effect.

Recently, several new factors have been identified and synthesized and are now being characterized and studied. They are potentially useful for therapy but scientists must first understand how they may influence neurons.

Since the destruction of neurons that use acetylcholine is one feature of Alzheimer's disease, any substance that can prevent this destruction is an important topic of research. NGF also holds promise for slowing the cognitive deficits associated with normal aging.

Once a neurotrophic factor for a particular cell type is found, copies can be genetically targeted to the area of the brain where this type of cell has died. The treatment probably will not cure a disease but will improve symptoms and delay progression.

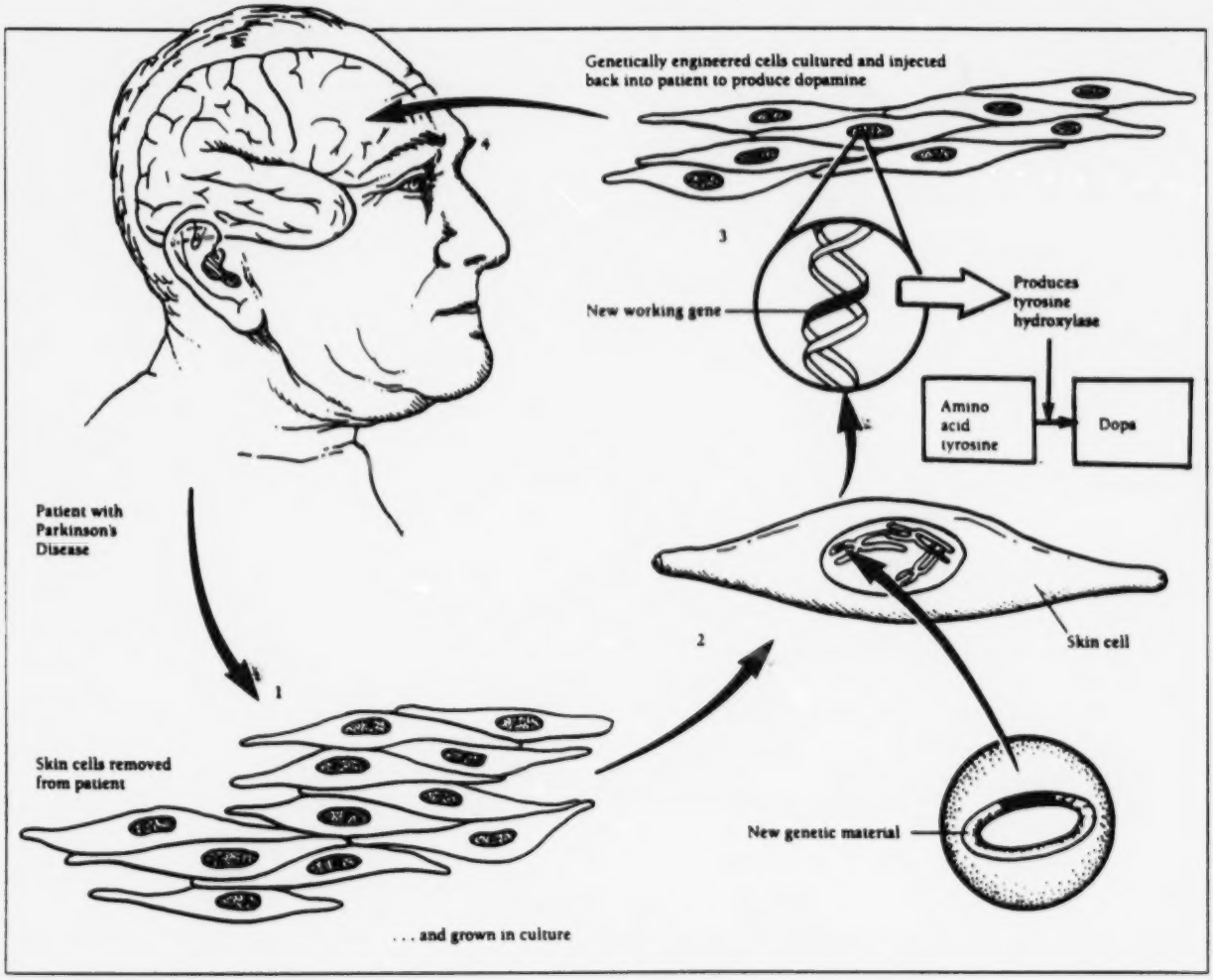
In an interesting twist on growth factor therapy, researchers have for the first time shown that an "anti-growth factor" can help repair damaged nerves. Using a genetically engineered antibody to proteins that inhibit nerve regeneration, Swiss researchers succeeded in getting nerves of severed spinal cords in rats to regrow.

In these experiments, scientists completely cut one of the major groups of nerves in the spinal cord that connect the spinal cord and the brain. When the genetically engineered protein IN-1 was injected into the brains of two- to six-week old rats, "massive sprouting" of nerve fibers occurred where the spinal cord had been cut. Within two to three weeks, neurons grew from about three-tenths of an inch to four-tenths of an inch. In untreated rats whose spinal cords were also cut, the maximum distance of regeneration rarely exceeded a tenth of an inch. This research could eventually lead to treatments to repair nerves damaged by accidents, strokes, peripheral nerve disorders and a wide variety of other nervous system diseases.

Transplants

Transplanting healthy neurons to take over the function of damaged neurons has also proved successful in animals. Scientists have reported reducing symptoms that mimic Parkinson's disease by injecting genetically altered skin cells into the brains of rats. The rat skin cells had been modified to produce dopa, the precursor of dopamine, a lack of which is believed to be a cause of Parkinson's.

Researchers took skin cells from rats and used a modified virus to insert genes that produce the enzyme



tyrosine hydroxylase. This enzyme converts a common amino acid, *tyrosine*, into dopa. Other enzymes in the brain convert dopa into dopamine.

The skin cells, converted into dopa factories, were injected into the brains of rats that had been purposely injured to cause neurological deterioration that mimics Parkinson's. Rats with this damage develop behavior that causes them to walk in circles. When the cells were transplanted into the brains of rats whose brains contained the lesions, the animals showed a 40 percent reduction in abnormal behavior.

Once perfected, this "indirect gene therapy" technique could be an alternative to fetal cell implants that have proved successful against Parkinson's in early research but raise moral and political questions about the ethics of their use.

Implantation of fetal cells secreting dopamine recently has been shown to slow the progression of Parkinson's in a single patient, a 49-year-old man with severe disease. In the procedure, brain cells from eight-to nine-week-old fetuses were mixed in a substance resembling body fluids. Then the solution was passed through a narrow tube directly into the brain of the patient so that the fetal cells, when implanted, matured into adult cells in an area where brain cells had been dying as a result of Parkinson's.

These are just a few examples of a broad range of opportunities neuroscientists are investigating for new therapies. In separate experiments, they are transplanting adrenal cells and olfactory neurons into the brain. In the future, computer-driven electronic implants may help restore vision and neuromuscular function.

GENE THERAPY. In one potential gene therapy technique, scientists plan to (1) remove skin cells from the body of a patient suffering from a neurological disorder such as Parkinson's disease. They then (2) insert into the skin cells genes that produce *tyrosine hydroxylase* which converts the common amino acid *tyrosine* into dopa, the precursor for dopamine, which is deficient in Parkinson's patients. The genetically engineered cells — now dopa factories — are then (3) selected for effectiveness and (4) injected back into the patient's brain where they will produce dopamine and, hopefully, improve symptoms.

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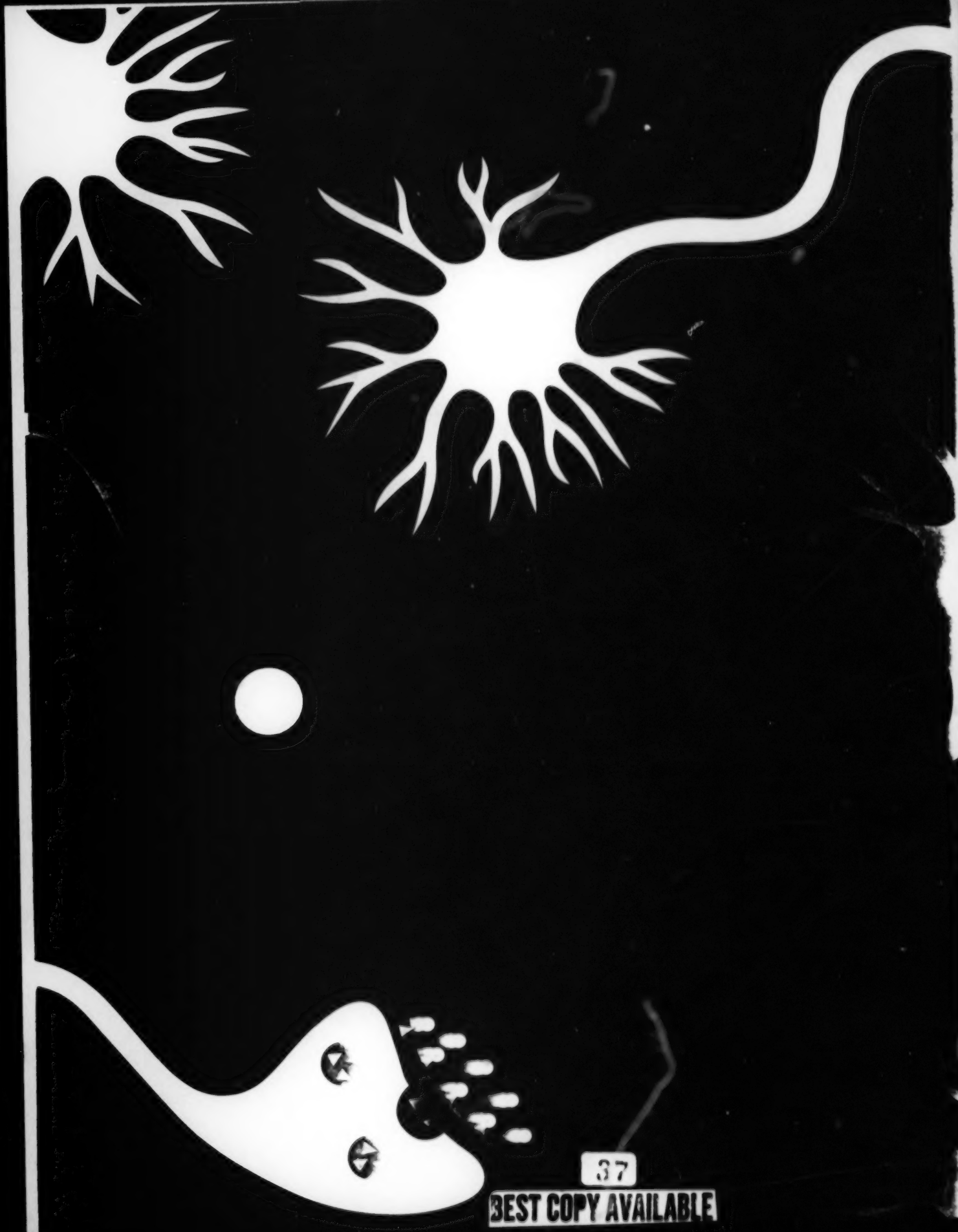

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